

5

FIELD OF THE INVENTION

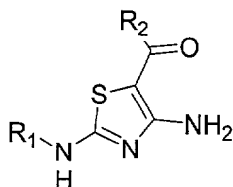
The present invention provides substituted triazole diamine derivatives as selective kinase or dual-kinase inhibitors and a method of use thereof. More particularly, the present invention provides substituted 1,2,4-triazole-3,5-diamine derivatives as selective kinase or dual-kinase inhibitors and a method for treating or ameliorating a selective kinase or dual-kinase mediated disorder.

BACKGROUND OF THE INVENTION

15

This Application claims priority from U.S. provisional patent application 60/257,703 entitled "1,2,4-triazole-3,5-diamine derivatives" filed December 22, 2000 the contents of which are hereby incorporated by reference.

Patent application WO 99/21845 describes 4-aminothiazole derivatives as inhibitors of cyclin dependent kinases of the formula:

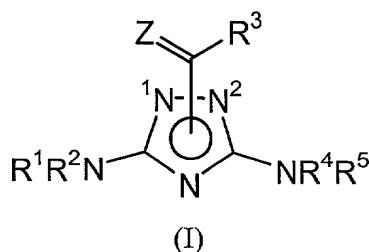


wherein

R₁ is a substituted or unsubstituted group selected from: C₁₋₆ alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl); C₁₋₆-alkenyl; C₁₋₆-alkynyl; C₁₋₆-alkoxy; C₁₋₆-alcohol; carbocyclic or heterocyclic cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl) or heterocycloalkyl, which may be monocyclic or fused or non-fused polycyclic (e.g., pyrrolidinyl, piperidinyl, morpholinyl); carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic aryl (e.g., phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl,

- triazolyl, tetrazolyl, pyrazolyl, pyridinyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzothiophenyl, or benzofuranyl); carbonyl (e.g., carboxyl, ester, aldehyde, or ketone); ether; (C₁₋₆ alkyl)-carbonyl; (C₁₋₆ alkyl)-aryl; (C₁₋₆ alkyl)-cycloalkyl; (C₁₋₆ alkyl)-(C₁₋₆-alkoxy); aryl-(C₁₋₆-alkoxy); thioether (e.g.,
- 5 aryl-S-aryl, cycloalkyl-S-aryl, cycloalkyl-S-cycloalkyl, or dialkyl sulfide); thiol; and sulfonyl; and R₂ is a substituted or unsubstituted: carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic, ring structure; where each optional substituent for R₁ and R₂ is independently a halogen (e.g., chloro, iodo, bromo, or fluoro); oxygen (=O); haloalkyl (e.g., trifluoromethyl); C₁₋₆ alkyl; C₁₋₆-alkenyl; C₁₋₆-alkynyl; hydroxyl; C₁₋₆-alkoxyl; carbocyclic cycloalkyl, which may be monocyclic or fused or non-fused polycyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), or a heterocycloalkyl, which may be monocyclic or fused or non-fused polycyclic (e.g., pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiazinyl); carbocyclic or heterocyclic, monocyclic or fused or non-fused polycyclic aryl (e.g.,
- 15 phenyl, naphthyl, pyrrolyl, indolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, pyrazolyl, pyridinyl, quinolinyl, isoquinolinyl, acridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzimidazolyl, benzothiophenyl, or benzofuranyl); amino (primary, secondary, or tertiary); nitro; thiol; thioether; imine; cyano; amido; phosphonato; phosphine; carboxyl; thiocarbonyl;
- 20 sulfonyl; sulfonamide; ketone; aldehyde; or ester; (ii) pharmaceutically acceptable salts of compounds of the Formula; and (iii) prodrugs and pharmaceutically active metabolites of compounds of the Formula or pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable carrier.

- 25 Patent application WO 01/09106 describes diamino-1,2,4-triazole-carboxylic and derivatives as GSK-3 (glycogen synthase kinase) inhibitors of formula (I):



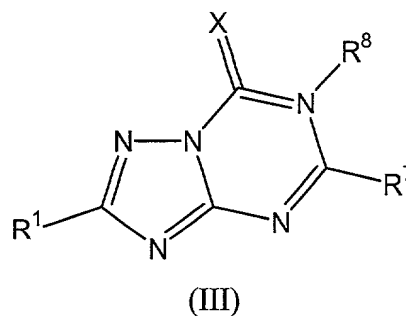
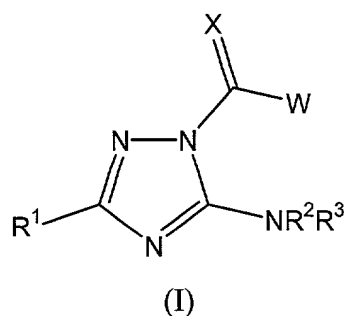
wherein

the R³CZ- moiety may be attached to the nitrogen atom at position I or the nitrogen

atom at position 2; R^1 is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic; R^2 is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or R^1 and R^2 together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted; R^3 is alkyl, aryl, aralkyl, aryl(Q)alkyl, where Q is O or S, aralkenyl, alicyclic, heteroaryl, heteroaralkyl, arylcarbonylalkyl, alicyclalkyl, diarylalkyl, or NR^6R^7 ; R^4 is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic; R^5 is hydrogen, alkyl, aryl, aralkyl, aralkenyl or alicyclic, or R^4 and R^5 together with the nitrogen atom to which they are attached may form a heterocyclic ring which ring may be unsubstituted or substituted; R^6 is hydrogen, aryl or alicyclic; R^7 is hydrogen, aryl or alicyclic, and; Z is oxygen or sulphur. Suitably, R^1 is hydrogen or unsubstituted or substituted phenyl, wherein the substituents for the phenyl group are independently selected from up to three of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy(C_1 - C_6)alkyl, aryl, aryloxy, halo, hydroxy, carboxy, cyano, and nitro. Favourably, R^1 is phenyl either unsubstituted or substituted with up to three of methyl, methoxy, or chloro. Suitably, R^2 is hydrogen or unsubstituted or substituted phenyl, wherein the substituents for the phenyl group are independently selected from up to three of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy(C_1 - C_6)alkyl, aryl, aryloxy, halo, hydroxy, carboxy, cyano, and nitro. Favourably, R^2 is hydrogen. Suitably, R^3 is unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or substituted benzyl, unsubstituted or substituted thienylmethyl, unsubstituted or substituted phenylthiomethyl, unsubstituted or substituted naphthylmethyl, unsubstituted or substituted furylethenyl, unsubstituted or substituted cyclohexyl, unsubstituted or substituted pyridyl, unsubstituted or substituted indolylmethyl, unsubstituted or substituted phenylcarbonylethyl, unsubstituted or substituted cyclopentenylmethyl, unsubstituted or substituted phenylpropyl, unsubstituted or substituted diphenylethyl, wherein the substituents for the R^3 aryl groups are selected from $-O(CH_2)_nO-$, where n is 1 to 3, or up to three of halo, aryl, perfluoro(C_1 - C_6)alkyl, nitro, arylcarbonyl, aryloxy, C_1 - C_6 acyl; or R^3 is NR^6R^7 where R^6 and R^7 are each independently hydrogen, unsubstituted or substituted aryl, or unsubstituted or substituted C_1 - C_6 alicyclic, wherein the substituents for the R^6 and R^7 groups are independently selected from up to three of halo, aryl, aryloxy, alkyl, nitro, and alkoxy. Favourably, R^3 is phenyl either unsubstituted or substituted with up to three of chloro, bromo, phenyl, trifluoromethyl, nitro, benzoyl, phenoxy, acetyl, or 3,4- OCH_2O- ; naphthyl; benzyl either unsubstituted or substituted

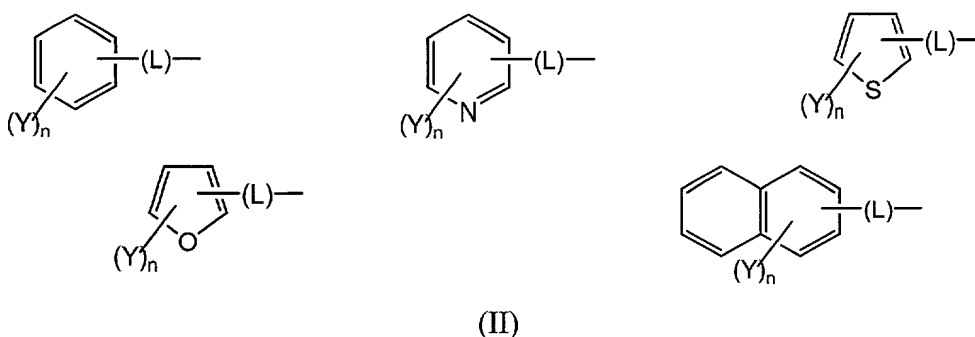
- with up to three of phenyl or fluoro; 2-thienylmethyl; phenylthiomethyl 2-naphthylmethyl; cyclohexyl; 3-pyridyl; 3-indolylmethyl; phenylcarbonylethyl; cyclopent-2-enylmethyl; phenylpropyl; 2,2-diphenylethyl; or 2-furylethenyl; or NR^6R^7 where R^6 and R^7 are each independently hydrogen, phenyl either unsubstituted or substituted with up to three of chloro, phenyl, phenoxy, methyl, bromo, nitro, or methoxy; cyclohexyl; or 1-naphthyl. Suitably, R^4 is hydrogen. Suitably, R^5 is hydrogen. Suitably, R^6 is unsubstituted or substituted aryl or unsubstituted or substituted alicyclic. Favourably R^6 is cyclohexyl, naphthyl or phenyl which phenyl group may be either unsubstituted or substituted with up to three of chloro, bromo, phenyl, methyl, phenoxy, nitro or methoxy. Suitably, R^7 is hydrogen.

United States Patent 5,750,545 describes triazole derivatives, as agents for the prophylaxis and treatment of immune-related diseases, of formula (I) and formula (III):



wherein

- 15 X is an oxygen atom or a sulfur atom; W is $-\text{NR}^4\text{R}^5$ or $-\text{SR}^6$; R^1 is a hydrogen atom, a lower alkyl, $-\text{NR}^{10}\text{R}^{11}$, $-\text{N}=\text{R}^{13}$ or a group of the formula (II)



wherein

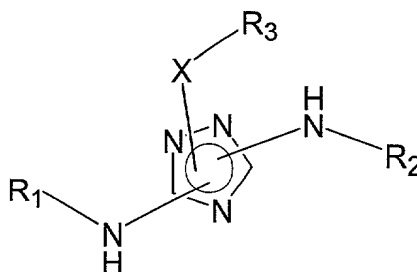
- Y is a hydrogen atom, a lower alkyl, a lower alkoxy, a halogen, a cyano, a nitro, a lower alkyl substituted by halogen, $-\text{NR}^{14}\text{R}^{15}$, a tetrazolyl, an optionally substituted phenyl, a hydroxy or a carboxyl, L is a direct bond, an oxygen atom, a sulfur atom, an alkylene, a vinylene or an ethynylene, and n is an integer of 1 to 3, provided that when n is 2 or 3,

Y may be the same or different; and R^2 and R^3 are the same or different and each is a hydrogen atom or a lower alkyl; wherein R^4 and R^5 are the same or different and each is a hydrogen atom, an optionally substituted lower alkyl, cycloalkyl, a phenyl or $-(CH_2)_mCOOR^{16}$, R^{16} is a hydrogen atom or a lower alkyl, m is an integer of 1 to 6, R^6 is a lower alkyl, R^{10} and R^{11} are the same or different and each is a hydrogen atom, an optionally substituted benzoyl, an optionally substituted phenyl, a lower alkylcarbonyl or $-COCOOR^{17}$, R^{17} is a lower alkyl, R^{13} is an optionally substituted methylene, R^{14} and R^{15} are the same or different and each is a hydrogen atom, a lower alkyl, $-COCOOR^{17}$ or $-CSNHR^{18}$, and R^{18} is a lower alkyl, or a pharmaceutically acceptable salt thereof.

Accordingly, it is an object of the present invention to provide substituted triazole diamine derivatives as selective kinase or dual-kinase inhibitors and a method of use thereof. It is an object of the present invention to provide substituted 1,2,4-triazole-3,5-diamine derivatives as selective kinase or dual-kinase inhibitors and a method of use for treating or ameliorating a selective kinase or dual-kinase mediated disorder.

SUMMARY OF THE INVENTION

The present invention provides a compound of Formula (I):



Formula (I)

wherein

R_1 is selected from the group consisting of C_{1-8} alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein heterocyclyl is optionally substituted with 1 to 2 oxo substituents; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are substituted with a substituent selected from the group consisting of:

C_{1-8} alkyl (optionally substituted on a terminal carbon with a substituent selected

from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

5

C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

-C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

10

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -SO₂-(C₁₋₈)alkyl),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

15

-SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen,

20

C₁₋₈alkyl, -C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl) and heteroaryl)},

cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; wherein heterocyclyl is optionally substituted with 1 to 2 oxo substituents; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with a substituent selected from the group consisting of C₁₋₈alkyl (wherein alkyl is

25

30

optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy and nitro), C₁₋₈alkoxy and amino (substituted with two substituents independently

selected from the group consisting of hydrogen and C₁₋₈alkyl}}};

R₂ is selected from the group consisting of hydrogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl and hydroxy(C₁₋₈)alkyl;

5

X is selected from the group consisting of -C(O)-, -C(S)- and -SO₂-; and,

R₃ is selected from the group consisting of:

10 C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, aryl and heteroaryl (wherein aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy and nitro)},

15

cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

20

C₁₋₈alkyl, C₂₋₈alkenyl (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

25

30 -CH(OH)-(C₁₋₈)alkyl,

C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

-C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

5 amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -C(O)(C₁₋₈)alkyl),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

10 -SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl))},

15 -NH-SO₂-(C₁₋₈)alkyl,

cycloalkyl, heterocyclyl (optionally substituted with 1 to 2 oxo substituents), aryl and heteroaryl} and

20 amino {substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, cycloalkyl, aryl and heteroaryl (wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy and nitro)};

25

and pharmaceutically acceptable salts thereof.

30 An embodiment of the present invention is a method for treating or ameliorating a selective kinase or dual-kinase mediated disorder.

An embodiment of the present invention includes a method for producing the

instant compounds and pharmaceutical compositions and medicaments thereof.

DETAILED DESCRIPTION OF THE INVENTION

- 5 Embodiments of the present invention include compounds of Formula (I) wherein, preferably, R_1 is selected from the group consisting of: C_{1-4} alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are substituted with a substituent selected from the group consisting of:
- 10 C_{1-4} alkyl (optionally substituted on a terminal carbon with a substituent selected from the group consisting of $-C(O)H$, $-C(O)(C_{1-4})alkyl$, $-CO_2H$, $-CO_2(C_{1-4})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, $(halo)_{1-3}$, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),
- 15 C_{1-4} alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy),
- $-C(O)H$, $-C(O)(C_{1-4})alkyl$, $-CO_2H$, $-CO_2(C_{1-4})alkyl$,
- 20 amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4} alkyl and $-SO_2-(C_{1-4})alkyl$,
- $-C(O)amino$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl),
- 25 $-SO_2-$ {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4} alkyl,
- 30 $-C_{1-4}alkylamino$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-4}alkyl$) and heteroaryl)},

cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; wherein heterocyclyl is optionally substituted with 1 to 2 oxo substituents; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with a substituent selected from the group consisting of C₁₋₄alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl), cyano, (halo)₁₋₃, hydroxy and nitro), C₁₋₄alkoxy and amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl)}}.

More preferably, R₁ is selected from the group consisting of C₁₋₄alkyl and aryl {wherein aryl is substituted with a substituent selected from the group consisting of:

C₁₋₄alkyl (optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl), cyano, (halo)₁₋₃, hydroxy and nitro),

C₁₋₄alkoxy,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₄alkyl and -SO₂-(C₁₋₄)alkyl),

-SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₄alkyl,

-C₁₋₄alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl) and heteroaryl)},

heterocyclyl (wherein heterocyclyl is optionally substituted with 1 to 2

substituents independently selected from the group consisting of C₁₋₄alkyl and oxo) and heteroaryl}.

Most preferably, R₁ is selected from the group consisting of C₁₋₄alkyl and phenyl
 5 {wherein phenyl is substituted with a substituent selected from the group consisting of:
 amino (substituted with two substituents independently selected from the group
 consisting of:

hydrogen, C₁₋₄alkyl and -SO₂-(C₁₋₄)alkyl),

10 -SO₂- {substituted with one substituent selected from the group consisting of
 piperidinyl and amino (wherein amino is substituted with two substituents
 independently selected from the group consisting of hydrogen, C₁₋₄alkyl,
 -C₁₋₄alkylamino (wherein amino is substituted with two substituents independently
 selected from the group consisting of hydrogen and C₁₋₄alkyl) and pyridinyl)}, and

15 piperazinyl (wherein piperazinyl is optionally substituted with 1 to 2 C₁₋₄alkyl
 substituents), imidazolidinyl, isothiazolidinyl (wherein imidazolidinyl and
 isothiazolidinyl are optionally substituted with 1 to 2 oxo substituents), imidazolyl
 and triazolyl}.

20 Embodiments of the present invention include compounds of Formula (I)
 wherein, preferably, R₂ is selected from the group consisting of hydrogen, C₁₋₄alkyl,
 C₂₋₄alkenyl, C₂₋₄alkynyl and hydroxy(C₁₋₄)alkyl.

25 More preferably, R₂ is selected from the group consisting of hydrogen and
 C₁₋₄alkyl.

Most preferably, R₂ is hydrogen.

30 Embodiments of the present invention include compounds of Formula (I)
 wherein, preferably, X is selected from the group consisting of -C(O)-, -C(S)- and
 -SO₂-.

Embodiments of the present invention include compounds of Formula (I) wherein, preferably, R_3 is selected from the group consisting of:

5 C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of $-C(O)H$, $-C(O)(C_{1-4})alkyl$, $-CO_2H$, $-CO_2(C_{1-4})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-4}alkyl$), cyano, $(halo)_{1-3}$, hydroxy, nitro, aryl and heteroaryl (wherein aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of $C_{1-4}alkyl$, cyano, halo, $(halo)_{1-3}(C_{1-4})alkyl$,
10 $(halo)_{1-3}(C_{1-4})alkoxy$, hydroxy, hydroxy($C_{1-4})alkyl$, hydroxy($C_{1-4})alkoxy$ and nitro)},

cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein
15 cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

$C_{1-4}alkyl$, $C_{2-4}alkenyl$ (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of
20 $-C(O)H$, $-C(O)(C_{1-4})alkyl$, $-CO_2H$, $-CO_2(C_{1-4})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-4}alkyl$), cyano, $(halo)_{1-3}$, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

25 $-CH(OH)-(C_{1-4})alkyl$,

$C_{1-4}alkoxy$ (optionally substituted on a terminal carbon with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy),

30 $-C(O)H$, $-C(O)(C_{1-4})alkyl$, $-CO_2H$, $-CO_2(C_{1-4})alkyl$,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, $C_{1-4}alkyl$ and $-C(O)(C_{1-4})alkyl$),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl),

5 -SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₄alkyl and -C₁₋₄alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl))},

10

-NH-SO₂-(C₁₋₄)alkyl,
cycloalkyl, heterocyclyl (optionally substituted with 1 to 2 oxo substituents),
aryl and heteroaryl} and

15

amino {substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₄alkyl, cycloalkyl, aryl and heteroaryl (wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₄alkyl, cyano, halo, (halo)₁₋₃(C₁₋₄)alkyl, (halo)₁₋₃(C₁₋₄)alkoxy, hydroxy, hydroxy(C₁₋₄)alkyl, hydroxy(C₁₋₄)alkoxy and nitro)}.

20

More preferably, R₃ is selected from the group consisting of:

C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group

25

consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, aryl and heteroaryl (wherein aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₄alkyl, cyano, halo, (halo)₁₋₃(C₁₋₄)alkyl, (halo)₁₋₃(C₁₋₄)alkoxy, hydroxy, hydroxy(C₁₋₄)alkyl,

30

hydroxy(C₁₋₄)alkoxy and nitro)},

cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the

group consisting of cyano, halo, hydroxy and nitro; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

5 C_{1-4} alkyl, C_{2-4} alkenyl (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of $-CO_2H$, $-CO_2(C_{1-4})$ alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

10 $-CH(OH)-(C_{1-4})$ alkyl,

C_{1-4} alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

15 $-C(O)H$, $-C(O)(C_{1-4})$ alkyl,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4} alkyl and $-C(O)(C_{1-4})$ alkyl),

20 aryl and heteroaryl} and

amino {substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-4} alkyl and aryl (wherein aryl is optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-4} alkyl, cyano, halo, (halo)₁₋₃(C_{1-4})alkyl, (halo)₁₋₃(C_{1-4})alkoxy, hydroxy, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy and nitro)}.

25

Most preferably, R_3 is selected from the group consisting of:

30 C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-4} alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, phenyl and thienyl (wherein phenyl and thienyl are optionally substituted with 1 to

2 substituents independently selected from the group consisting of C₁₋₄alkyl, cyano, halo, hydroxy and nitro}},

cyclopentyl, cyclohexyl, cycloheptyl, benzo[*b*]thienyl, phenyl, furyl, thienyl, thiazolyl, isoxazolyl, thiadiazolyl, pyridinyl {wherein cyclohexyl and phenyl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein cyclohexyl and phenyl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

C₁₋₄alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl), cyano, (halo)₁₋₃, hydroxy and nitro),

-CH(OH)-(C₁₋₄)alkyl,

C₁₋₄alkoxy,

amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl),

and wherein thienyl and thiazolyl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein thienyl and thiazolyl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

C₁₋₄alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of -CO₂H, -CO₂(C₁₋₄)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl), cyano, (halo)₁₋₃, hydroxy and nitro),

C₁₋₄alkoxy,

-C(O)(C₁₋₄)alkyl,

amino (substituted with two substituents independently selected from the group consisting of: hydrogen, C₁₋₄alkyl and -C(O)(C₁₋₄)alkyl),

5

pyrrolyl and pyridinyl;

and, wherein thiadiazolyl is optionally substituted with one substituent selected from the group consisting of C₁₋₄alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of:

10

amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl), cyano, (halo)₁₋₃, hydroxy and nitro), C₁₋₄alkoxy, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl),

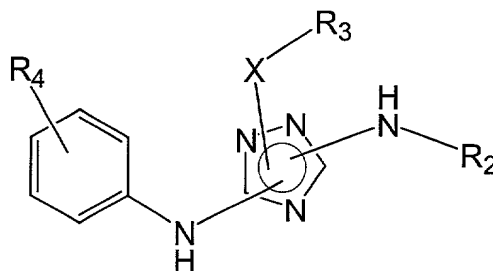
15

cyano, halo, hydroxy and nitro} and

amino {substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₄alkyl and phenyl (wherein phenyl is optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₄alkyl, cyano, halo, hydroxy and nitro)}.

20

Embodiments of the present invention include compounds of Formula (I) selected from a compound of Formula (Ia):



Formula (Ia)

25 wherein

R₄ is selected from the group consisting of:

C₁₋₈alkyl {optionally substituted on a terminal carbon with a substituent selected from

the group consisting of $-C(O)H$, $-C(O)(C_{1-8})alkyl$, $-CO_2H$, $-CO_2(C_{1-8})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$), cyano, $(halo)_{1-3}$, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl},

- 5 $C_{1-8}alkoxy$ (optionally substituted on a terminal carbon with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy),
 $-C(O)H$, $-C(O)(C_{1-8})alkyl$, $-CO_2H$, $-CO_2(C_{1-8})alkyl$,
 amino (substituted with two substituents independently selected from the group consisting of hydrogen, $C_{1-8}alkyl$ and $-SO_2-(C_{1-8})alkyl$),
- 10 $-C(O)amino$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$),
 $-SO_2-$ {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, $C_{1-8}alkyl$,
- 15 $-C_{1-8}alkylamino$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$) and heteroaryl},
 cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of $C_{1-8}alkyl$ (wherein alkyl is optionally substituted on a
- 20 terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$), cyano, $(halo)_{1-3}$, hydroxy and nitro), $C_{1-8}alkoxy$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$), cyano, halo, hydroxy and nitro; and, wherein
- 25 heterocyclyl is optionally substituted with 1 to 2 oxo substituents};

R_2 is selected from the group consisting of hydrogen, $C_{1-8}alkyl$, $C_{2-8}alkenyl$, $C_{2-8}alkynyl$ and hydroxy(C_{1-8})alkyl;

- 30 X is selected from the group consisting of $-C(O)-$, $-C(S)-$ and $-SO_2-$; and,

R_3 is selected from the group consisting of:

$C_{1-8}alkyl$, $C_{2-8}alkenyl$, $C_{2-8}alkynyl$ {wherein alkyl, alkenyl and alkynyl are optionally

substituted on a terminal carbon with a substituent selected from the group consisting of $-C(O)H$, $-C(O)(C_{1-8})alkyl$, $-CO_2H$, $-CO_2(C_{1-8})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$), cyano, $(halo)_{1-3}$, hydroxy, nitro, aryl and heteroaryl (wherein aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of $C_{1-8}alkyl$, cyano, halo, $(halo)_{1-3}(C_{1-8})alkyl$, $(halo)_{1-3}(C_{1-8})alkoxy$, hydroxy, hydroxy($C_{1-8})alkyl$, hydroxy($C_{1-8})alkoxy$ and nitro)}, cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

$C_{1-8}alkyl$, $C_{2-8}alkenyl$ (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of

$-C(O)H$, $-C(O)(C_{1-8})alkyl$, $-CO_2H$, $-CO_2(C_{1-8})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$), cyano, $(halo)_{1-3}$, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

$-CH(OH)-(C_{1-8})alkyl$,

$C_{1-8}alkoxy$ (optionally substituted on a terminal carbon with a substituent selected from the group consisting of $(halo)_{1-3}$ and hydroxy),

$-C(O)H$, $-C(O)(C_{1-8})alkyl$, $-CO_2H$, $-CO_2(C_{1-8})alkyl$,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, $C_{1-8}alkyl$ and $-C(O)(C_{1-8})alkyl$),

$-C(O)amino$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$),

$-SO_2-$ {substituted with one substituent selected from the group consisting of

heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl))),

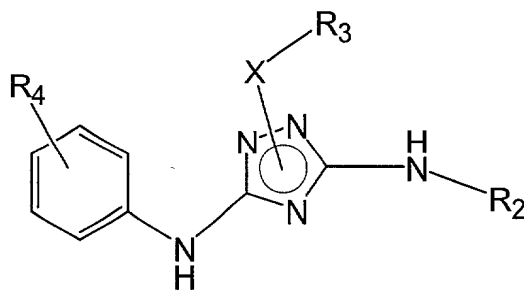
5

-NH-SO₂-(C₁₋₈)alkyl,
cycloalkyl, heterocyclyl (optionally substituted with 1 to 2 oxo substituents), aryl and heteroaryl} and

- 10 amino {substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, cycloalkyl, aryl and heteroaryl (wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl,
15 hydroxy(C₁₋₈)alkoxy and nitro)};

and pharmaceutically acceptable salts thereof.

- Embodiments of the present invention include compounds of Formula (I)
20 selected from a compound of Formula (Ib):



Formula (Ib)

wherein

R₄ is selected from the group consisting of:

- C₁₋₈alkyl {optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino
25 (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl},

C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

-C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

amino (substituted with two substituents independently selected from the group

5 consisting of hydrogen, C₁₋₈alkyl and -SO₂-(C₁₋₈)alkyl),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

-SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents

10 independently selected from the group consisting of hydrogen, C₁₋₈alkyl,

-C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl) and heteroaryl)},

cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected

15 from the group consisting of C₁₋₈alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy and nitro), C₁₋₈alkoxy, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, halo, hydroxy and nitro; and, wherein

20 heterocyclyl is optionally substituted with 1 to 2 oxo substituents};

R₂ is selected from the group consisting of hydrogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl and hydroxy(C₁₋₈)alkyl;

25

X is selected from the group consisting of -C(O)-, -C(S)- and -SO₂-; and,

R₃ is selected from the group consisting of:

30 C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, aryl and heteroaryl (wherein aryl and

heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C_{1-8} alkyl, cyano, halo, $(\text{halo})_{1-3}(C_{1-8})\text{alkyl}$, $(\text{halo})_{1-3}(C_{1-8})\text{alkoxy}$, hydroxy, hydroxy(C_{1-8})alkyl, hydroxy(C_{1-8})alkoxy and nitro}}, cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and

5 heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

10 C_{1-8} alkyl, C_{2-8} alkenyl (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})(C_{1-8})\text{alkyl}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2(C_{1-8})\text{alkyl}$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl), cyano, $(\text{halo})_{1-3}$, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

15 $-\text{CH}(\text{OH})-(C_{1-8})\text{alkyl}$,

C_{1-8} alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of $(\text{halo})_{1-3}$ and hydroxy),

20 $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})(C_{1-8})\text{alkyl}$, $-\text{CO}_2\text{H}$, $-\text{CO}_2(C_{1-8})\text{alkyl}$,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl and $-\text{C}(\text{O})(C_{1-8})\text{alkyl}$),

25 $-\text{C}(\text{O})\text{amino}$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C_{1-8} alkyl),

30 $-\text{SO}_2-$ {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C_{1-8} alkyl and $-\text{C}_{1-8}\text{alkylamino}$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}\text{alkyl}$))}},

-NH-SO₂-(C₁₋₈)alkyl,

cycloalkyl, heterocyclyl (optionally substituted with 1 to 2 oxo substituents),

5 aryl and heteroaryl} and

amino {substituted with two substituents independently selected from the group

consisting of hydrogen, C₁₋₈alkyl, cycloalkyl, aryl and heteroaryl (wherein

cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents

10 independently selected from the group consisting of C₁₋₈alkyl, cyano, halo,

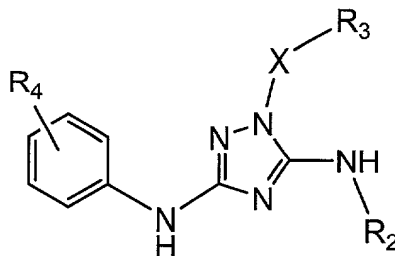
(halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl,

hydroxy(C₁₋₈)alkoxy and nitro)};

and pharmaceutically acceptable salts thereof.

15

Embodiments of the present invention include compounds of Formula (I)
selected from a compound of Formula (Ic):



Formula (Ic)

wherein

R₄ is selected from the group consisting of:

20 C₁₋₈alkyl {optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl},

25 C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),
-C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -SO₂-(C₁₋₈)alkyl),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

- 5 -SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, -C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl) and heteroaryl)},
- 10 cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy and nitro), C₁₋₈alkoxy, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, halo, hydroxy and nitro; and, wherein
- 15 heterocyclyl is optionally substituted with 1 to 2 oxo substituents};
- 20 R₂ is selected from the group consisting of hydrogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl and hydroxy(C₁₋₈)alkyl;

X is selected from the group consisting of -C(O)-, -C(S)- and -SO₂-; and,

- 25 R₃ is selected from the group consisting of: C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, aryl and heteroaryl (wherein aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy and nitro)},
- 30

cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

C_{1-8} alkyl, C_{2-8} alkenyl (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of $-C(O)H$, $-C(O)(C_{1-8})alkyl$, $-CO_2H$, $-CO_2(C_{1-8})alkyl$, amino (substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

$-CH(OH)-(C_{1-8})alkyl$,

$C_{1-8}alkoxy$ (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

$-C(O)H$, $-C(O)(C_{1-8})alkyl$, $-CO_2H$, $-CO_2(C_{1-8})alkyl$,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, $C_{1-8}alkyl$ and $-C(O)(C_{1-8})alkyl$),

$-C(O)amino$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$),

$-SO_2-$ {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, $C_{1-8}alkyl$ and $-C_{1-8}alkylamino$ (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and $C_{1-8}alkyl$)))},

$-NH-SO_2-(C_{1-8})alkyl$,

cycloalkyl, heterocyclyl (optionally substituted with 1 to 2 oxo substituents), aryl and heteroaryl} and

amino {substituted with two substituents independently selected from the group

- 5 consisting of hydrogen, C₁₋₈alkyl, cycloalkyl, aryl and heteroaryl (wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy and nitro));

10

and pharmaceutically acceptable salts thereof.

Embodiments of the present invention include compounds of Formula (Ic) wherein, preferably, R₄ is selected from the group consisting of:

15

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₄alkyl and -SO₂-(C₁₋₄)alkyl),

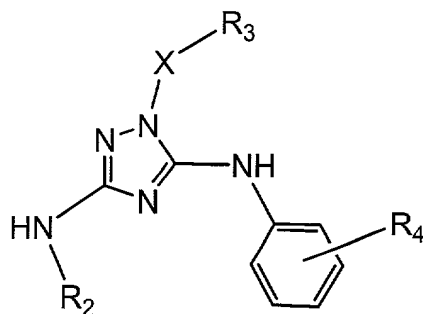
-SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₄alkyl, -C₁₋₄alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₄alkyl) and heteroaryl)},

20

- 25 heterocyclyl (wherein heterocyclyl is optionally substituted with 1 to 2 substituents independently selected from the group consisting of C₁₋₄alkyl and oxo) and heteroaryl.

Embodiments of the present invention include compounds of Formula (I) selected from a compound of Formula (Id):

30



Formula (Id)

wherein

R₄ is selected from the group consisting of:

C₁₋₈alkyl {optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl},

C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

-C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -SO₂-(C₁₋₈)alkyl),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

-SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl,

-C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl) and heteroaryl)},

cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy and nitro), C₁₋₈alkoxy, amino (substituted with two substituents independently selected from the group consisting

of hydrogen and C₁₋₈alkyl), cyano, halo, hydroxy and nitro; and, wherein heterocyclyl is optionally substituted with 1 to 2 oxo substituents};

- 5 R₂ is selected from the group consisting of hydrogen, C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl and hydroxy(C₁₋₈)alkyl;

X is selected from the group consisting of -C(O)-, -C(S)- and -SO₂-; and,

R₃ is selected from the group consisting of:

- 10 C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, aryl and heteroaryl (wherein aryl and
- 15 heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy and nitro)}, cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected
- 20 from the group consisting of cyano, halo, hydroxy and nitro; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:
- C₁₋₈alkyl, C₂₋₈alkenyl (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of
- 25 -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),
- 30 -CH(OH)-(C₁₋₈)alkyl,

C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

-C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

5 amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -C(O)(C₁₋₈)alkyl),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

10 -SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl))},

15 -NH-SO₂-(C₁₋₈)alkyl,

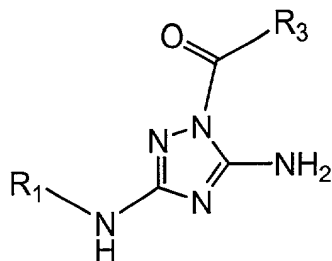
cycloalkyl, heterocyclyl (optionally substituted with 1 to 2 oxo substituents), aryl and heteroaryl} and

20 amino {substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, cycloalkyl, aryl and heteroaryl (wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy and nitro)};

25

and pharmaceutically acceptable salts thereof.

30 Embodiments of the present invention include compounds of Formula (I) selected from a compound of Formula (Ie):



Formula (Ie)

wherein

R₁ is selected from the group consisting of C₁₋₈alkyl,

cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein heterocyclyl is optionally substituted with 1 to 2 oxo substituents; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are substituted with a substituent selected from the group consisting of:

C₁₋₈alkyl (optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

-C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -SO₂-(C₁₋₈)alkyl),

-C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

-SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, -C₁₋₈alkylamino (wherein amino is substituted with two substituents

independently selected from the group consisting of hydrogen and C₁₋₈alkyl) and heteroaryl)},

cycloalkyl, heterocyclyl, aryl and heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; wherein heterocyclyl is optionally substituted with 1 to 2 oxo substituents; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with a substituent selected from the group consisting of C₁₋₈alkyl (wherein alkyl is optionally substituted on a terminal carbon with a substituent selected from the group consisting of amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy and nitro), C₁₋₈alkoxy and amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl)}; and,

R₃ is selected from the group consisting of:

C₁₋₈alkyl, C₂₋₈alkenyl, C₂₋₈alkynyl {wherein alkyl, alkenyl and alkynyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, aryl and heteroaryl (wherein aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl, hydroxy(C₁₋₈)alkoxy and nitro)}, cycloalkyl, heterocyclyl, aryl, heteroaryl {wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 3 substituents independently selected from the group consisting of cyano, halo, hydroxy and nitro; and, wherein cycloalkyl, heterocyclyl, aryl and heteroaryl are optionally substituted with 1 to 2 substituents independently selected from the group consisting of:

C₁₋₈alkyl, C₂₋₈alkenyl (wherein alkyl and alkenyl are optionally substituted on a terminal carbon with a substituent selected from the group consisting of -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl, amino (substituted with two

substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl), cyano, (halo)₁₋₃, hydroxy, nitro, cycloalkyl, heterocyclyl, aryl and heteroaryl),

5 -CH(OH)-(C₁₋₈)alkyl,

C₁₋₈alkoxy (optionally substituted on a terminal carbon with a substituent selected from the group consisting of (halo)₁₋₃ and hydroxy),

10 -C(O)H, -C(O)(C₁₋₈)alkyl, -CO₂H, -CO₂(C₁₋₈)alkyl,

amino (substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -C(O)(C₁₋₈)alkyl),

15 -C(O)amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl),

20 -SO₂- {substituted with one substituent selected from the group consisting of heterocyclyl and amino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl and -C₁₋₈alkylamino (wherein amino is substituted with two substituents independently selected from the group consisting of hydrogen and C₁₋₈alkyl))},

25 -NH-SO₂-(C₁₋₈)alkyl,

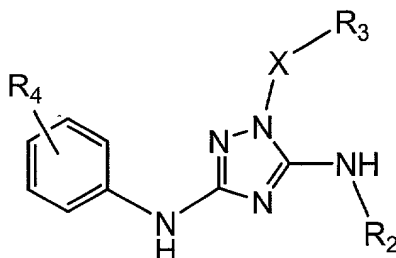
cycloalkyl, heterocyclyl (optionally substituted with 1 to 2 oxo substituents), aryl and heteroaryl} and

30 amino {substituted with two substituents independently selected from the group consisting of hydrogen, C₁₋₈alkyl, cycloalkyl, aryl and heteroaryl (wherein cycloalkyl, aryl and heteroaryl are optionally substituted with 1 to 5 substituents independently selected from the group consisting of C₁₋₈alkyl, cyano, halo, (halo)₁₋₃(C₁₋₈)alkyl, (halo)₁₋₃(C₁₋₈)alkoxy, hydroxy, hydroxy(C₁₋₈)alkyl,

hydroxy(C₁₋₈)alkoxy and nitro));

and pharmaceutically acceptable salts thereof.

- 5 Exemplified compounds of the present invention include a compound of Formula (I) selected from a compound of Formula (Ic):



Formula (Ic)

wherein X, R₂, R₃ and R₄ are dependently selected from:

Cpd	X	R ₂	R ₃	R ₄
1	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ -NH ₂
2	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-SO ₂ -NH ₂
3	C(O)	H	(2,4,6-F ₃)Ph	4-SO ₂ -NH ₂
4	C(O)	H	(2-F)Ph	4-SO ₂ -NH ₂
5	C(O)	H	(2,4-F ₂)Ph	4-SO ₂ -NH ₂
6	C(O)	H	(2-F-6-CF ₃)Ph	4-SO ₂ -NH ₂
7	C(O)	H	(2,6-Cl ₂)Ph	4-SO ₂ -NH ₂
8	C(O)	H	(2,4,6-Cl ₃)Ph	4-SO ₂ -NH ₂
9	C(O)	H	(2-NO ₂)Ph	4-SO ₂ -NH ₂
10	C(O)	H	[2,6-(OCH ₃) ₂]Ph	4-SO ₂ -NH ₂
11	C(O)	H	[2,4,6-(CH ₃) ₃]Ph	4-SO ₂ -NH ₂
12	C(O)	H	Ph	4-SO ₂ -NH ₂
13	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ -1- <i>H</i> -piperidin-1-yl
14	C(O)	H	2-thienyl	4-SO ₂ -NH ₂
15	C(O)	H	(3-CH ₃)2-thienyl	4-SO ₂ -NH ₂
16	C(O)	H	(3-F)2-thienyl	4-SO ₂ -NH ₂
17	C(O)	H	(3-Cl)2-thienyl	4-SO ₂ -NH ₂
18	C(O)	H	(3-OCH ₂ CH ₃)2-thienyl	4-SO ₂ -NH ₂
19	C(O)	H	(3-NHCOCH ₃)2-thienyl	4-SO ₂ -NH ₂
20	C(O)	H	(5-CH ₃)2-thienyl	4-SO ₂ -NH ₂

21	C(O)	H	(5-Br)2-thienyl	4-SO ₂ -NH ₂
22	C(O)	H	(5-COCH ₃)2-thienyl	4-SO ₂ -NH ₂
23	C(O)	H	2-thienyl	4-SO ₂ -1- <i>H</i> -piperidin-1-yl
24	C(O)	H	(3-CH ₃)2-thienyl	4-SO ₂ -1- <i>H</i> -piperidin-1-yl
25	C(O)	H	2-furyl	4-SO ₂ -NH ₂
26	C(O)	H	5-isoxazolyl	4-SO ₂ -NH ₂
27	C(O)	H	2-pyridinyl	4-SO ₂ -NH ₂
28	C(O)	H	3-pyridinyl	4-SO ₂ -NH ₂
29	C(O)	H	4-pyridinyl	4-SO ₂ -NH ₂
30	C(O)	H	3-thienyl	4-SO ₂ -NH ₂
31	C(O)	H	3a,7a-dihydrobenzo[<i>b</i>]thien-2-yl	4-SO ₂ -NH ₂
32	C(O)	H	(5-CH ₂ CH ₃)2-thienyl	4-SO ₂ -NH ₂
33	C(O)	H	[3,5-(CH ₃) ₂]2-thienyl	4-SO ₂ -NH ₂
34	C(O)	H	[2,4-(CH ₃) ₂]5-thiazolyl	4-SO ₂ -NH ₂
35	C(O)	H	(3-Br)2-thienyl	4-SO ₂ -NH ₂
36	C(O)	H	4-(CH ₃)-1,2,3-thiadiazol-5-yl	4-SO ₂ -NH ₂
37	C(O)	H	1,2,3-thiadiazol-4-yl	4-SO ₂ -NH ₂
38	C(O)	H	cyclopentyl	4-SO ₂ -NH ₂
39	C(O)	H	cyclohexyl	4-SO ₂ -NH ₂
40	C(O)	H	2-thienyl-CH ₂	4-SO ₂ -NH ₂
42	C(O)	H	2-thienyl-(CH) ₂	4-SO ₂ -NH ₂
43	C(O)	H	(2,6-F ₂)-Ph-CH ₂	4-SO ₂ -NH ₂
44	C(O)	H	(2,6-F ₂)Ph(CH) ₂	4-SO ₂ -NH ₂
45	C(O)	H	cycloheptyl	4-SO ₂ -NH ₂
46	C(O)	H	4-CH ₃ -cyclohexyl	4-SO ₂ -NH ₂
47	C(O)	H	4-CH ₃ -cyclohexyl	4-SO ₂ -NH ₂
48	C(O)	H	4-(CH ₂) ₃ CH ₃ -cyclohexyl	4-SO ₂ -NH ₂
49	C(O)	H	5-(2-pyridinyl)2-thienyl	4-SO ₂ -NH ₂
50	C(O)	H	3-(1 <i>H</i> -pyrrol-1-yl)2-thienyl	4-SO ₂ -NH ₂
51	C(O)	H	5-[C(CH ₃) ₃]2-thienyl	4-SO ₂ -NH ₂
52	C(O)	H	5-[(CH) ₂ C(O)OC(CH ₃) ₃]2-thienyl	4-SO ₂ -NH ₂

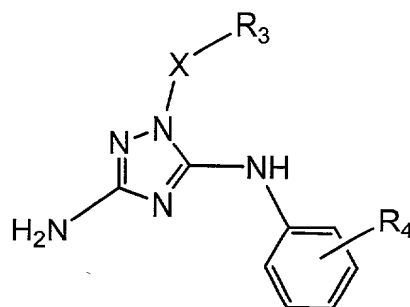
53	C(O)	H	Ph(C) ₂	4-SO ₂ -NH ₂
54	C(O)	H	(2,6-F ₂ -3-NO ₂)Ph	4-SO ₂ -NH ₂
55	C(O)	H	(2,6-F ₂ -3-NH ₂)Ph	4-SO ₂ -NH ₂
56	C(O)	H	[2,6-(CH ₃) ₂]Ph	4-SO ₂ -NH ₂
57	C(O)	H	(2-CH ₃)Ph	4-SO ₂ -NH ₂
58	C(O)	H	[2,6-F ₂ -3-CH(OH)CH ₃]Ph	4-SO ₂ -NH ₂
59	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ -NH ₂
60	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-SO ₂ -NH ₂
61	C(O)	H	(2,6-F ₂)Ph	H
62	C(O)	H	Ph	H
63	C(O)	H	(2,6-F ₂)Ph	3-Cl
64	C(O)	H	Ph	3-Cl
65	C(O)	H	-NH(Ph)	H
66	C(S)	H	-NH[(2,6-F ₂)Ph]	4-SO ₂ -NH ₂
67	C(O)	H	-NH[(2,6-F ₂)Ph]	4-SO ₂ -NH ₂
68	SO ₂	H	(2,6-F ₂)Ph	4-SO ₂ -NH ₂
69	C(O)	H	(2-Cl-3-CH ₃ -6-F)Ph	4-SO ₂ -NH ₂
70	C(O)	H	(2-Cl-6-F)Ph	4-SO ₂ -NH ₂
71	C(O)	H	(2,6-F ₂)Ph	4-(4-CH ₃ -1,4- <i>H</i> -piperazin-1-yl)
72	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-(4-CH ₃ -1,4- <i>H</i> -piperazin-1-yl)
73	C(O)	H	(3-CH ₃) ₂ -thienyl	4-(4-CH ₃ -1,4- <i>H</i> -piperazin-1-yl)
74	C(O)	H	[3,5-(CH ₃) ₂] ₂ -thienyl	4-(4-CH ₃ -1,4- <i>H</i> -piperazin-1-yl)
75	C(O)	H	(5-CH ₂ CH ₃) ₂ -thienyl	4-(4-CH ₃ -1,4- <i>H</i> -piperazin-1-yl)
76	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ -NH(CH ₂ CH ₃)
78	C(O)	H	(2,6-F ₂ -5-Cl)Ph	4-SO ₂ -NH ₂
80	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ -NH(CH ₃)
81	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-SO ₂ -NH(CH ₃)
82	C(O)	H	(3-CH ₃) ₂ -thienyl	4-SO ₂ -NH(CH ₃)
83	C(O)	H	[3,5-(CH ₃) ₂] ₂ -thienyl	4-SO ₂ -NH(CH ₃)
84	C(O)	H	(5-CH ₂ CH ₃) ₂ -thienyl	4-SO ₂ -NH(CH ₃)
85	C(O)	H	[3,5-(CH ₃) ₂] ₂ -thienyl	4-SO ₂ -N(CH ₃) ₂

86	C(O)	H	(5-CH ₂ CH ₃)2-thienyl	4-SO ₂ -N(CH ₃) ₂
87	C(O)	H	(3-CH ₃)2-thienyl	4-SO ₂ -N(CH ₃) ₂
88	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-SO ₂ -N(CH ₃) ₂
89	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ -N(CH ₃) ₂
90	C(O)	H	(5-CH ₂ CH ₃)2-thienyl	4-(1- <i>H</i> -imidazol-1-yl)
91	C(O)	H	(3-CH ₃)2-thienyl	4-(1- <i>H</i> -imidazol-1-yl)
92	C(O)	H	[3,5-(CH ₃) ₂]2-thienyl	4-(1- <i>H</i> -imidazol-1-yl)
93	C(O)	H	(2,6-F ₂)Ph	4-(1- <i>H</i> -imidazol-1-yl)
94	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-(1- <i>H</i> -imidazol-1-yl)
95	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-(1- <i>H</i> -1,2,4-triazol-1-yl)
96	C(O)	H	(2,6-F ₂)Ph	4-(1- <i>H</i> -1,2,4-triazol-1-yl)
97	C(O)	H	(5-CH ₂ CH ₃)2-thienyl	4-(1- <i>H</i> -1,2,4-triazol-1-yl)
98	C(O)	H	[3,5-(CH ₃) ₂]2-thienyl	4-(1- <i>H</i> -1,2,4-triazol-1-yl)
99	C(O)	H	(3-CH ₃)2-thienyl	4-(1- <i>H</i> -1,2,4-triazol-1-yl)
100	C(O)	H	(2,6-F ₂)Ph	4-(1- <i>H</i> -1,3,4-triazol-1-yl)
101	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-(1- <i>H</i> -1,3,4-triazol-1-yl)
102	C(O)	H	(3-CH ₃)2-thienyl	4-(1- <i>H</i> -1,3,4-triazol-1-yl)
103	C(O)	H	(5-CH ₂ CH ₃)2-thienyl	4-SO ₂ - NH[(CH ₂) ₂ N(CH ₃) ₂]
104	C(O)	H	(3-CH ₃)2-thienyl	4-SO ₂ - NH[(CH ₂) ₂ N(CH ₃) ₂]
105	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-SO ₂ - NH[(CH ₂) ₂ N(CH ₃) ₂]
106	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ - NH[(CH ₂) ₂ N(CH ₃) ₂]
107	C(O)	H	[3,5-(CH ₃) ₂]2-thienyl	4-SO ₂ - NH[(CH ₂) ₂ N(CH ₃) ₂]
108	C(O)	H	[3,5-(CH ₃) ₂]2-thienyl	4-NH-SO ₂ -CH ₃
109	C(O)	H	(3-CH ₃)2-thienyl	4-NH-SO ₂ -CH ₃
110	C(O)	H	(5-CH ₂ CH ₃)2-thienyl	4-NH-SO ₂ -CH ₃
111	C(O)	H	(2,6-F ₂)Ph	4-NH-SO ₂ -CH ₃
112	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-NH-SO ₂ -CH ₃
113	C(O)	H	(3-CH ₃)2-thienyl	4-(2-imidazolidinone)
114	C(O)	H	(2,6-F ₂ -3-CH ₃)Ph	4-(2-imidazolidinone)
115	C(O)	H	(2,6-F ₂)Ph	4-(2-imidazolidinone)

116	C(O)	H	(3-CH ₃) ₂ -thienyl	4-(1,1-dioxido-2-isothiazolidinyl)
117	C(O)	H	(2,6-F ₂)Ph	4-(1,1-dioxido-2-isothiazolidinyl)
118	C(O)	H	(2,6-F ₂)Ph	4-SO ₂ -NH-2-pyridinyl
119	C(O)	H	(5-CH ₂ CH ₃) ₂ -thienyl	4-SO ₂ -NH-2-pyridinyl
120	C(O)	H	[3,5-(CH ₃) ₂]-2-thienyl	4-SO ₂ -NH-2-pyridinyl
and,				
121	C(O)	H	(3-CH ₃) ₂ -thienyl	4-SO ₂ -NH-2-pyridinyl

and pharmaceutically acceptable salts thereof.

Exemplified compounds of the present invention include a compound of Formula (I) selected from a compound of Formula (Id):



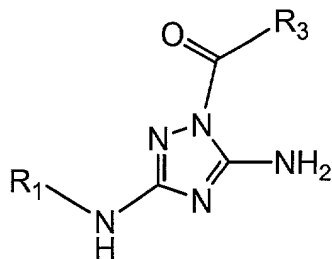
Formula (Id)

5 wherein X, R₃ and R₄ are dependently selected from:

Cpd	X	R ₃	R ₄
122	C(O)	(2,6-F ₂)Ph	4-SO ₂ -NH ₂
123	C(O)	(2,6-F ₂ -3-CH ₃)Ph	4-SO ₂ -NH ₂
124	C(O)	(2,6-F ₂)Ph	H
125	C(O)	Ph	H
126	C(O)	(2,6-F ₂)Ph	3-Cl
127	C(O)	Ph	3-Cl
and,			
128	C(S)	-NH[(2,6-F ₂)Ph]	4-SO ₂ -NH ₂

and pharmaceutically acceptable salts thereof.

Exemplified compounds of the present invention include a compound of Formula (I) selected from a compound of Formula (Ie):



Formula (Ie)

wherein R_1 and R_3 are dependently selected from:

Cpd	R_1	R_3
79	CH_3	(3- CH_3)2-thienyl

and pharmaceutically acceptable salts thereof.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts" (*Ref. International J. Pharm.*, 1986, 33, 201-217; *J. Pharm.Sci.*, 1997 (Jan), 66, 1, 1). Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds, which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the subject.

Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

5 Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques
10 such as preparative chromatography. The compounds may be prepared in racemic form or individual enantiomers may be prepared by standard techniques known to those skilled in the art, for example, by enantiospecific synthesis or resolution, formation of diastereomeric pairs by salt formation with an optically active acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be
15 resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention and moreover that the term "a compound of Formula x" will encompass a compound's
20 enantiomers, diastereomers, and the like.

 Unless specified otherwise, the term "alkyl" refers to a saturated straight or branched chain consisting solely of 1-8 hydrogen substituted carbon atoms; preferably, 1-6 hydrogen substituted carbon atoms; and, most preferably, 1-4 hydrogen substituted
25 carbon atoms. The term "alkenyl" refers to a partially unsaturated straight or branched alkyl chain that contains at least one double bond. The term "alkynyl" refers to a partially unsaturated straight or branched alkyl chain that contains at least one triple bond. The term "alkoxy" refers to -O-alkyl, where alkyl is as defined *supra*.

30 The term "cycloalkyl" refers to a saturated or partially unsaturated cyclic alkyl ring consisting of 3-8 hydrogen substituted carbon atoms. Examples include, and are not limited to, cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "heterocyclyl" refers to a saturated or partially unsaturated ring having five members of which at least one member is a N, O or S atom and which optionally contains one additional O atom or one, two or three additional N atoms; a saturated or partially unsaturated ring having six members of which one, two or three members are a N atom; a saturated or partially unsaturated bicyclic ring having nine members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms; and, a saturated or partially unsaturated bicyclic ring having ten members of which one, two or three members are a N atom. Examples include, and are not limited to, pyrrolinyl, pyrrolidinyl, dioxolanyl, imidazoliny, imidazolidinyl, pyrazoliny, pyrazolidinyl, piperidinyl, morpholinyl or piperazinyl.

The term "aryl" refers to an aromatic monocyclic ring system containing 6 hydrogen substituted carbon atoms, an aromatic bicyclic ring system containing 10 hydrogen substituted carbon atoms or an aromatic tricyclic ring system containing 14 hydrogen substituted carbon atoms. Examples include, and are not limited to, phenyl, naphthalenyl or anthracenyl.

The term "heteroaryl" refers to an aromatic monocyclic ring system containing five members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms, an aromatic monocyclic ring having six members of which one, two or three members are a N atom, an aromatic bicyclic ring having nine members of which at least one member is a N, O or S atom and which optionally contains one, two or three additional N atoms and an aromatic bicyclic ring having ten members of which one, two or three members are a N atom. Examples include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, indazolyl, quinolinyl or isoquinolinyl.

The term "halo" or "halogen" refers to a fluoro, chloro, bromo or iodo atom.

"Independently" means that when a group is substituted with more than one substituent that the substituents may be the same or different. "Dependently" means that the substituents are specified in an indicated combination of structure variables.

An embodiment of the invention is a pharmaceutical composition or medicament comprising a pharmaceutically acceptable carrier and any of the compounds described above. Illustrative of the invention is a pharmaceutical composition or medicament made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Another illustration of the invention is a process for making a pharmaceutical composition or medicament comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. Further illustrative of the present invention are pharmaceutical compositions or medicaments comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The compounds of the present invention are selective kinase or dual-kinase inhibitors useful in a method for treating or ameliorating a kinase or dual-kinase mediated disorder. In particular, the kinase is selected from a cyclin dependent kinase and a tyrosine kinase. More particularly, the kinase is selected from cyclin dependent kinase-1, cyclin dependent kinase-2, cyclin dependent kinase-4, vascular endothelial growth factor receptor-2, endothelial growth factor receptor or human epidermal growth factor receptor-2.

Cyclin-dependent kinase inhibitors play a critical role in regulating progression of the eukaryotic cell through the cell cycle by associating with protein complexes composed of cyclins and cyclin- dependent kinases and thus down-regulating the activity of the cyclin- dependent kinases. Pathways involving cyclin-dependent kinase inhibitors are frequently disrupted in tumor cells leading to abnormal regulation of the cell cycle. Overexpression of cyclin- dependent kinase inhibitors leads to arrest of cells at one of the check points in the cell cycle. Therefore, using cyclin-dependent kinase inhibitors for tumor therapy is intuitively attractive because it has the potential for

tumour growth. Inhibition or for the inhibition or control of uncontrolled cell proliferation such as occurs in some angiopathies, benign tumor growth, leukemias, and the like. A particularly good CDK inhibitor target for the design of anti-tumor agents is the CDK-1 receptor. This protein controls the last checkpoint in the cell cycle between the G2 and M phase.

A second protein target that can facilitate elimination of a tumor is the tyrosine kinase vascular endothelial growth factor (VEGF) receptor. This protein is associated with both normal and pathological angiogenesis. The VEGF receptors are tripartite, consisting of an extracellular ligand-binding domain, a transmembrane domain and an intracellular tyrosine kinase domain. Presently there are two known VEGF receptors: (1) VEGF-R2 (KDR/Flk1/VEGF-R2), a receptor that mediates the biological activities of mitogenesis and proliferation of endothelial cells; and (2) VEGF-R1 (Flt1/VEGF-R1), a receptor that mediates functions such as endothelial cell adhesion. Inhibition of VEGF-R2 signalling has been shown to inhibit the process of angiogenesis. Inhibitors of this receptor are likely useful in controlling or limiting angiogenesis.

Many conventional cytotoxic cancer therapies destroy the rapidly dividing epithelium of the hair follicle and induce alopecia (hair loss). Inhibition of cyclin dependent kinases may represent a therapeutic strategy for prevention of chemotherapy-induced alopecia by arresting the cell cycle and reducing the sensitivity of epithelial cells to antitumor agents (Davis S.T., et al., Prevention of chemotherapy-induced alopecia in rats by CDK inhibitors, *Science*, **2001**, (Jan 5), 291, 5501, 25-6). Topical application of non-apoptotic CDK inhibitors represents a potentially useful approach for the prevention of chemotherapy-induced alopecia in cancer patients.

Although coronary angioplasty is a highly effective procedure used to reduce the severity of coronary occlusion, its long-term success is limited by a high rate of restenosis. Vascular smooth muscle cell activation, migration, and proliferation is largely responsible for restenosis following angioplasty (Ross, R., *Nature*, **1993**, 362, 801-809). Recent studies have shown that CDK2 is activated very early after endothelial denudation in a rat carotid artery model of restenosis (Wei, G. L., et al.,

Circ. Res., 1997, 80, 418–426). Therefore, antiproliferative therapies targeted to cyclin dependent kinases or other components of the cell cycle machinery may be a suitable approach to treat these disorders.

5 Embodiments of the method of the present invention include a method for treating or ameliorating a selective kinase or dual-kinase mediated disorder in a subject in need thereof comprising administering to the subject a therapeutically effective amount of an instant compound or pharmaceutical composition thereof. The therapeutically effective amount of the compounds of Formula (I) exemplified in such a
10 method is from about 0.001 mg/kg/day to about 300 mg/kg/day.

 Embodiments of the present invention include the use of a compound of Formula (I) for the preparation of a medicament for treating or ameliorating a kinase or dual-kinase mediated disorder in a subject in need thereof.

15 In accordance with the methods of the present invention, an individual compound of the present invention or a pharmaceutical composition thereof can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The instant invention is therefore to be
20 understood as embracing all such regimes of simultaneous or alternating treatment and the term “administering” is to be interpreted accordingly.

 Embodiments of the present method include a compound or pharmaceutical composition thereof advantageously co-administered in combination with other agents
25 for treating or ameliorating a kinase or dual-kinase mediated disorder. The combination product comprises co-administration of a compound of Formula (I) or pharmaceutical composition thereof and an additional agent for treating or ameliorating a kinase or dual-kinase mediated disorder, the sequential administration of a compound of Formula (I) or pharmaceutical composition thereof and an additional agent for
30 treating or ameliorating a kinase or dual-kinase mediated disorder, administration of a pharmaceutical composition containing a compound of Formula (I) or pharmaceutical composition thereof and an additional agent for treating or ameliorating a kinase or dual-kinase mediated disorder or the essentially simultaneous administration of a

separate pharmaceutical composition containing a compound of Formula (I) or pharmaceutical composition thereof and a separate pharmaceutical composition containing an additional agent for treating or ameliorating a kinase or dual-kinase mediated disorder.

5

The term "other agents" includes, and is not limited to, anti-angiogenic agents, anti-tumor agents, cytotoxic agents, inhibitors of cell proliferation, and the like. The term "treating or ameliorating" includes, and is not limited to, facilitating the eradication of, inhibiting the progression of or promoting stasis of a malignancy. For example, a dual CDK1-VEGF-R inhibitor compound of the present invention, acting as an anti-angiogenic agent can be administered in a dosing regimen with at least one other cytotoxic compound, such as a DNA alkylating agent. Preferred anti-tumor agents are selected from the group consisting of cladribine (2-chloro-2'-deoxy-(beta)-D-adenosine), Chlorambucil (4-[bis(2-chlorethyl)amino]benzenebutanoic acid), DTIC-Dome (5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide), platinum chemotherapeutics and nonplatinum chemotherapeutics. Platinum containing anti-tumor agents include, but are not limited to, cisplatin (cis-dichlorodiamineplatinum). Non-platinum containing anti-tumor agents include, but are not limited to, cyclophosphamide, fluorouracil, epirubicin, methotrexate, vincristine, doxorubicin, bleomycin, and etoposide. Each anti-tumor agent is administered in a therapeutically effective amount, which varies based on the agent used, the type of malignancy to be treated or ameliorated and other conditions, according to methods well known in the art.

25

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

30

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

The ubiquitous nature of the kinase isoforms and their important roles in physiology provide incentive to produce highly selective kinase inhibitors. Given the evidence demonstrating linkage of certain isoforms to disease states, it is reasonable to assume that inhibitory compounds that are selective to one or two isoforms (those compounds selective to at least two cyclin dependent kinase or tyrosine kinase isoforms are referred to as dual kinase inhibitors) or to a single isoform relative to other isoforms and other kinases are superior therapeutic agents. Such compounds should demonstrate greater efficacy and lower toxicity by virtue of their specificity. Accordingly, it will be appreciated by one skilled in the art that a compound of Formula (I) is therapeutically effective for certain kinase or dual-kinase mediated disorders based on the modulation of the disorder by selective kinase or dual-kinase inhibition. The activity of the instant compounds as selective kinase or dual-kinase inhibitors is derived from the novel combination of the structural elements X, R₃ and R₄ optimally substituted on the triazole scaffold. The usefulness of a compound of Formula (I) as a selective kinase or dual-kinase inhibitor can be determined according to the methods disclosed herein and the scope of such usefulness includes use in one or more kinase or dual-kinase mediated disorders.

Therefore, the term “kinase or dual-kinase mediated disorders” as used herein, includes, and is not limited to compounds capable of inhibiting one or more kinases where kinase inhibition is also associated with cancers, abnormal cell proliferation, tumor growth, tumor vascularization, as well as angiopathy, angiogenesis, chemotherapy-induced alopecia and restenosis.

The compounds of this invention are useful as an adjunct to a variety of chemotherapeutic agents that are recommended for specific cancer therapy regimes. For example, the compounds of this invention have been demonstrated to be useful in combination therapies with at least one other chemotherapeutic agent for the treatment of a number of different cancers and advantageously appears to facilitate the use of a reduced dose of the chemotherapeutic agent that is recommended for a particular cancer or cell proliferation disorder. Therefore, it is contemplated that the compounds of this invention can be used in a treatment regime before the administration of a particular

chemotherapeutic agent recommended for the treatment of a particular cancer, during administration of the chemotherapeutic agent or after treatment with a particular chemotherapeutic agent.

5 Pharmaceutical compositions contemplated within this invention can be prepared according to conventional pharmaceutical techniques. A pharmaceutically acceptable carrier may be used in the composition of the invention. The composition may take a wide variety of forms depending on the form of preparation desired for administration including, but not limited to, intravenous (both bolus and infusion), oral,
10 nasal, transdermal, topical with or without occlusion, intraperitoneal, subcutaneous, intramuscular or parenteral, all using forms well known to those of ordinary skill in the pharmaceutical arts. In preparing the compositions in oral dosage form, one or more of the usual pharmaceutical carriers may be employed, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, syrup and the like in the case
15 of oral liquid preparations (for example, suspensions, elixirs and solutions), or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (for example, powders, capsules and tablets).

20 As is also known in the art, the compounds may alternatively be administered parenterally via injection of a formulation consisting of the active ingredient dissolved in an inert liquid carrier. The injectable formulation can include the active ingredient mixed with an appropriate inert liquid carrier. Acceptable liquid carriers include vegetable oils such as peanut oil, cotton seed oil, sesame oil, and the like, as well as
25 organic solvents such as solketal, glycerol, formal, and the like. As an alternative, aqueous parenteral formulations may also be used. For example, acceptable aqueous solvents include water, Ringer's solution and an isotonic aqueous saline solution. Further, a sterile non-volatile oil can usually be employed as solvent or suspending agent in the aqueous formulation. The formulations are prepared by dissolving or
30 suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.005 to 10% by weight of the active ingredient. Other additives including a preservative, an isotonizer, a solubilizer, a stabilizer and a pain-soothing agent may adequately be employed.

Furthermore, compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

Because of their ease of administration, tablets and capsules represent an advantageous oral dosage unit form, wherein solid pharmaceutical carriers are employed. If desired, tablets may be sugarcoated or enteric-coated by standard techniques.

For liquid forms the active drug component can be combined in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, including for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents that may be employed include glycerin and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes containing delivery systems as well known in the art are formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

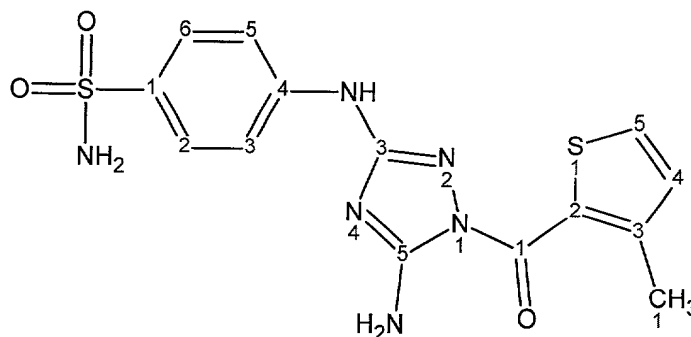
The instant pharmaceutical composition will generally contain a per dosage unit (e.g., tablet, capsule, powder, injection, teaspoonful and the like) from about 0.001 to about 100 mg/kg. In one embodiment, the instant pharmaceutical composition contains a per dosage unit of from about 0.01 to about 50 mg/kg of compound, and preferably from about 0.05 to about 20 mg/kg. Methods are known in the art for determining therapeutically effective doses for the instant pharmaceutical composition. The therapeutically effective amount for administering the pharmaceutical composition to a human, for example, can be determined mathematically from the results of animal studies.

Abbreviations

	"Cpd"	Compound
	"CSCl ₂ "	thiophosgene
	"DIC"	diisopropyl carbodiimide
5	"DMF"	N,N-dimethylformamide
	"EDCI"	ethyl dimethylaminopropyl carbodiimide
	"HOBT"	hydroxybenzyl triazole
	"NH ₂ NH ₂ "	hydrazine
	"Pd"	palladium(II)
10	"Ph"	phenyl
	"rt"	room temperature
	"TBAF"	tetrabutylammonium fluoride
	"TFA"	trifluoroacetic acid
15	"THF"	tetrahydrofuran

Nomenclature

Compounds are named according to nomenclature well known in the art, as exemplified using ring numbering as follows:



4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide.

Names can be generated using a nomenclature system based on this example, or may be generated using commercial chemical naming software such as ACD/Index Name (Advanced Chemistry Development, Inc., Toronto, Ontario).

General Synthetic Methods

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are illustrations, the

invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

5

Scheme A

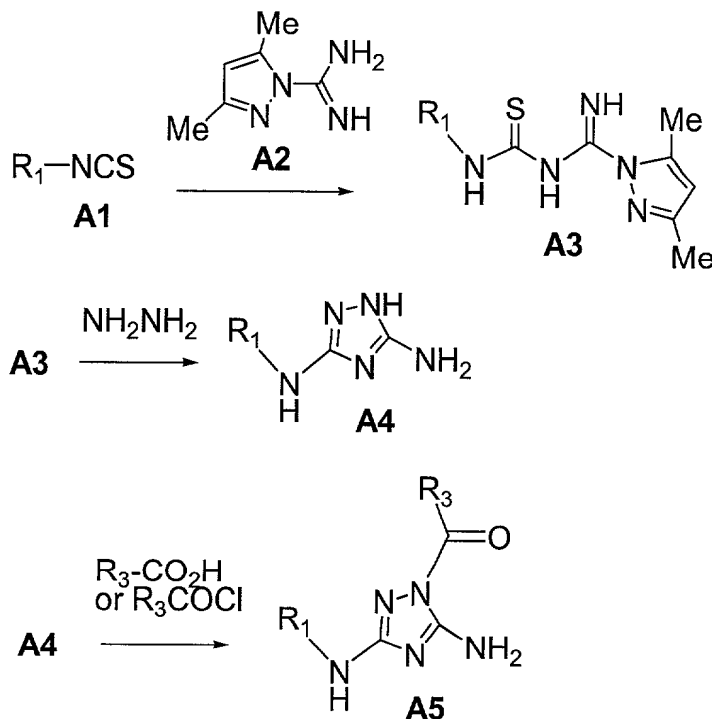
To prepare a Compound **A3** (as described in Jenardanan, G. C., Francis, M., Deepa, S., and Rajaskekharan, N. R., *Synthetic Communications*, **1997**, 27, 19, 3457-3462), the isocyanate Compound **A1** (prepared according to R. L. McKee and R. W. Bost, *J. Am. Chem. Soc.*, **1946**, 68, 2506-2507) (wherein R_1 is as previously defined) was dissolved in a suitable solvent and combined with a suspension of Compound **A2** and potassium hydroxide in solvent. The mixture was warmed and stirred and the product Compound **A3** was isolated by precipitation in cold water.

10

To prepare a Compound **A5** (Reiter, J., Pongo, L. and Dvortsak, P., *J. Heterocyclic Chemistry*, **1987**, 24, 127-142), Compound **A3** was dissolved in a suitable solvent and reacted with hydrazine. The solvent was then evaporated and the residue of Compound **A3** was refluxed in an alcohol solvent to produce a solid Compound **A4**. Compound **A4** was dissolved in a suitable solvent and reacted with R_3CO_2H or R_3COCl (wherein R_3 is as previously defined) and a coupling reagent such as DIC (diisopropyl carbodiimide) or EDCI (ethyl dimethylaminopropyl carbodiimide) to yield the target Compound **A5**.

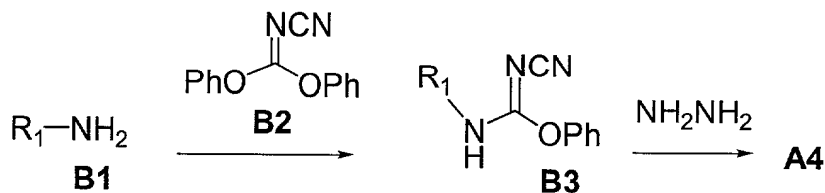
15

20



Scheme B

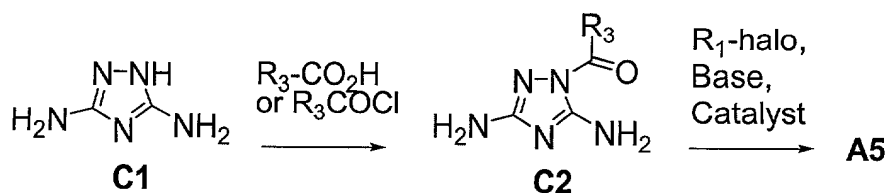
Alternatively, Compound **B3** was prepared according to published procedure (as described in Webb, R. L., Eggleston, D. S. and Labaw, C. S., *J. Heterocyclic Chemistry*, 1987, 24, 275-278). Following the procedure of Scheme A, Compound **B3** was reacted with hydrazine to produce the target intermediate Compound **A4**.



Scheme C

Compound **C1** (CAS # 1455-77-2) was dissolved in a suitable solvent and reacted with R_3CO_2H or R_3COCl (wherein R_3 is as previously defined) and a coupling reagent such as DIC or EDCI to yield the Compound **C2**. Compound **C2** was purified, dissolved in a suitable solvent and reacted in an inert atmosphere with R_1 -halo (wherein R_1 and halo are as previously defined; in addition to halo, R_1 may be coupled with another suitable leaving group) in the presence of a base, such as potassium carbonate, and a catalyst, such as a palladium complex. The product Compound **A5** was isolated using

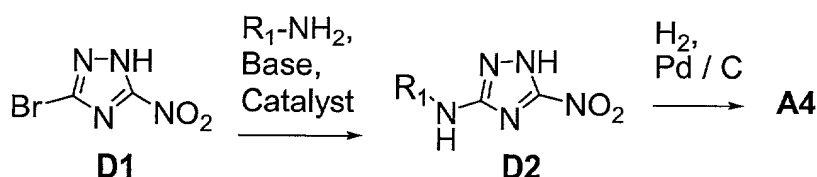
conventional means.



5

Scheme D

Alternatively, Compound **D1** (CAS# 24807-56-5) was dissolved in a suitable solvent and reacted with R_1NH_2 in the presence of a base such as potassium carbonate, and a catalyst such as a palladium complex to yield the Compound **D2**. Compound **D2** was purified, dissolved in a suitable solvent and subjected to catalytic hydrogenation to give Compound **A4**. Compound **A4** may then be used to produce other target compounds of the invention as described in Scheme A.

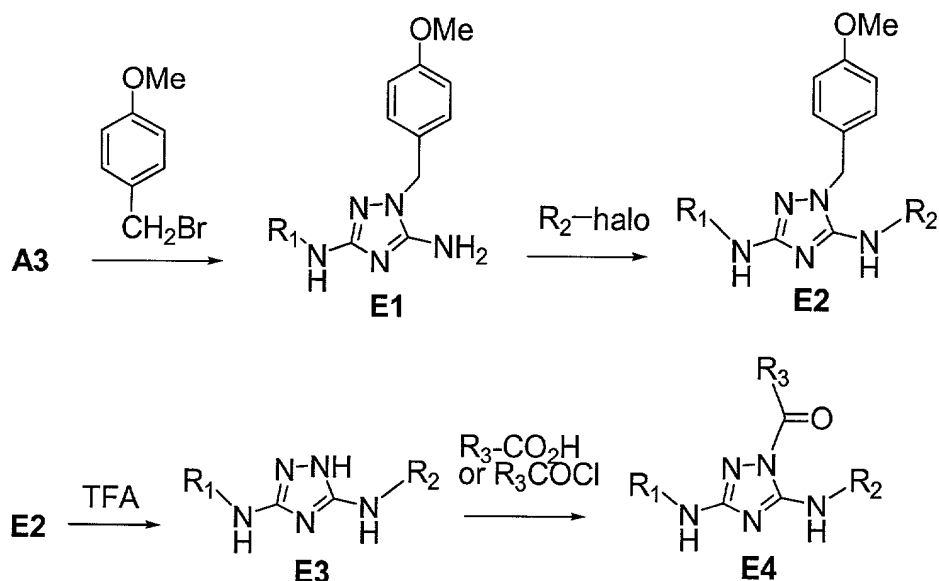


15

Scheme E

Compound **A3** was dissolved in a solvent and reacted with a protecting group such as a substituted benzyl halide (for example, 4-methoxybenzyl bromide) in the presence of a base (such as potassium carbonate) to yield a Compound **E1**. Compound **E1** was purified, dissolved in a suitable solvent and then reacted with $\text{R}_2\text{-halo}$ (wherein R_2 and halo are as previously defined; in addition to halo, R_2 may be coupled with another suitable leaving group) in the presence of a base (such as potassium carbonate) to give a Compound **E2**. Compound **E2** was treated with a suitable reagent, such as trifluoroacetic acid, which upon heating produced Compound **E3**. Compound **E3** was dissolved in a suitable solvent and reacted with $\text{R}_3\text{CO}_2\text{H}$ or R_3COCl (wherein R_3 is as previously defined) and a coupling reagent such as DIC or EDCI to yield a target Compound **E4**. The product Compound **E4** was purified using conventional means.

25



Alternatively, to prepare a Compound **E4**, Compound **A5** was dissolved in a suitable solvent and reacted with $\text{R}_2\text{-halo}$ (wherein R_2 and halo are as previously defined; in addition to halo, R_2 may be coupled with another suitable leaving group) in the presence of a base (such as potassium carbonate).

Specific Synthetic Examples

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The depicted intermediates may also be used in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

^1H and ^{13}C NMR spectra were measured on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane and DMSO respectively as internal standards. Elemental analyses were obtained by Quantitative Technologies Inc. (Whitehouse, New Jersey), and the results were within 0.4% of the calculated values unless otherwise mentioned. Melting points were determined in open capillary tubes with a Mel-Temp II apparatus

(Laboratory Devices Inc.) and were uncorrected. Electrospray mass spectra (MS-ES) were recorded on a Hewlett Packard 59987A spectrometer.

Example 1

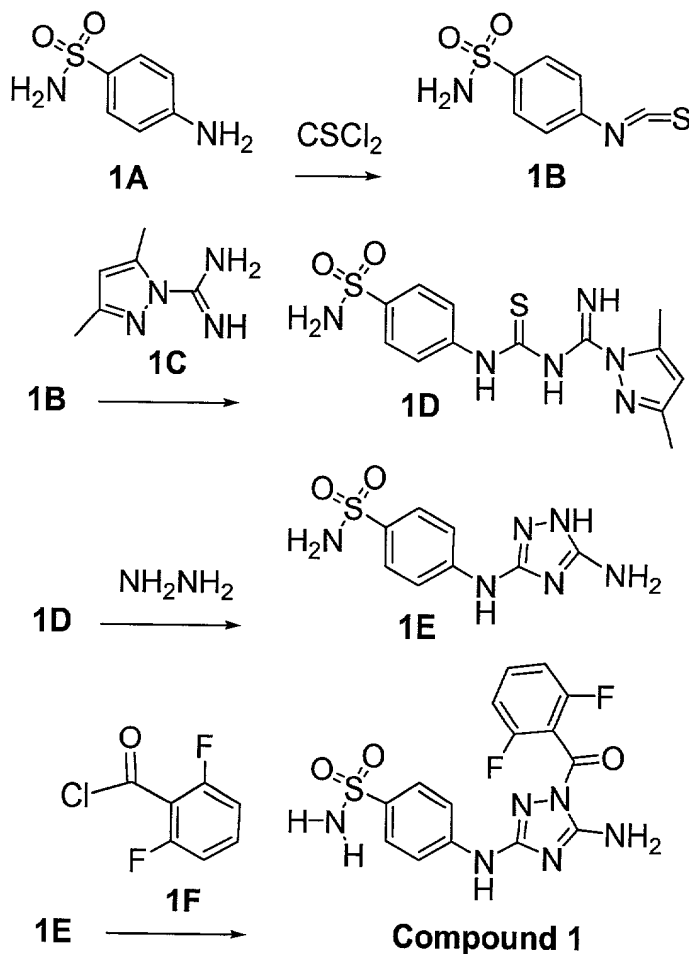
5 4-[[5-amino-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide (Cpd 1)

A suspension of 1-amidino-3,5-dimethylpyrazole nitrate Compound 1C (2.012 g, 10 mmol) and potassium hydroxide powder (0.561g, 10 mmol) in DMF (8 mL) at 0 °C was added to a DMF solution (3 mL) of isocyanate Compound 1B (prepared from
10 sulfanilamide Compound 1A and thiophosgene according to R. L. McKee and R. W. Bost, *J. Am. Chem. Soc.*, **1946**, 68, 2506-2507). The reaction mixture was warmed up to 50-60 °C, stirred for 1 h, and then poured into 250 ml of icy water. The resultant yellow solid was filtered, rinsed with water and dried *in vacuo* to give an intermediate Compound 1D as yellow powder (2.5513 g); m.p. 69-80 °C (decomposed); ¹H NMR
15 (300 MHz, CD₃OD) δ 7.90 (m, 4H), 6.05 (s, 1H), 2.22 (s, 3H), 2.20 (s, 3H); (CDCl₃) δ 10.75 (s, br, 1H), 8.35 (s, br, 1H), 7.90 (q, 4H), 7.65 (s, br, 2H), 5.95 (s, 1H), 5.00 (s, br, 2H); MS (ESI) m/z: 353 (M+H⁺).

Hydrazine (1.845 g, 57.58 mmol) was added to a solution of the intermediate
20 Compound 1D (1.88 g, 5.33 mmol) in THF (60 mL). The reaction mixture was stirred vigorously at 50-60 °C for 2-3 hours, and then evaporated *in vacuo*. The residue was then refluxed in methanol (60 mL) and cooled down to rt. The resultant solid was collected by filtration and rinsed with methanol to produce intermediate Compound 1E as a gray solid (0.8722 g, 64%). m.p. 291 - 296 °C (decomposed); ¹H NMR (300 MHz,
25 (CD₃)₂SO) δ 9.20 (s, 1H), 7.60 (m, 4H), 7.00 (s, 2H), 5.90 (s, 2H); MS (ESI) m/z: 255 (M+H⁺), 277 (M+Na⁺).

2,6-difluorobenzoyl chloride Compound 1F (41.4 uL, 0.33 mmol) was added to a solution of the intermediate Compound 1E (63.6 mg, 0.25 mmol) dissolved in
30 anhydrous pyridine (2.5 mL) in an ice-water bath. The resulting reaction mixture was stirred at rt for 6 hours, and then evaporated *in vacuo* to dryness. Chromatography purification of the residue with 10% methanol/methylene chloride and recrystallization from THF/methylene chloride gave Compound 1 (50.2 mg, 51%) as a white powder.

m.p. 149 - 155 °C (decomposed); ^1H NMR (300 MHz, CD_3OD) δ 7.65 (m, 3H), 7.55 (d, 2H), 7.18 (t, 2H); ($(\text{CD}_3)_2\text{SO}$) δ 9.86 (s, 1H), 8.03 (s, 2H), 7.72 (m, 1H), 7.58 (d, $J = 8.9$ Hz, 2H), 7.46 (d, $J = 8.9$ Hz, 2H), 7.35 (t, $J = 8.3$ Hz, 2H), 7.11 (s, 2H); ^{13}C NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ 160.4, 159.7, 158.9, 157.9, 157.1, 157.0, 156.6, 144.0, 135.6, 133.9, 127.0, 116.3, 112.9, 112.5, 112.3; MS (ESI) m/z : 395 ($\text{M}+\text{H}^+$), 417 ($\text{M}+\text{Na}^+$). Anal. Calcd. For $\text{C}_{15}\text{H}_{12}\text{F}_2\text{N}_6\text{O}_3\text{S}$: C, 45.69; H, 3.07; N, 21.31. Found: C, 45.29; H, 3.04; N, 20.89.



Using the procedure for Example 1, the following compounds were prepared by acylation of the intermediate Compound 1E using the indicated starting material in place of Compound 1F and reagent(s):

Cpd	Name/Data	Starting Mat'l
-----	-----------	----------------

- | | | |
|---|---|---|
| 2 | 4-[[5-amino-1-(2,6-difluoro-3-methylbenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.80 (s, 1H), 7.78-7.55 (m, 5H), 7.52 (s, 2H), 7.12 (t, 2H), 6.38 (s, 2H), 2.22 (s, 3H); MS (ESI) m/z: 409 (M+H ⁺), 431 (M+Na ⁺) | 2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine |
| 3 | 4-[[5-amino-1-(2,3,6-trifluorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.85 (s, 1H), 7.78-7.50 (m, 7H), 7.32 (m, 1H), 6.38 (s, 2H); MS (ESI) m/z: 413 (M+H ⁺), 435 (M+Na ⁺) | 2,3,6-trifluorobenzoyl chloride in anhydrous pyridine |
| 4 | 4-[[5-amino-1-(2-fluorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.90 (s, br, 1H), 8.00 (s, br, 2H), 7.82 (t, 1H), 7.78-7.20 (m, 7H), 6.35 (s, br, 2H); MS (ESI) m/z: 377 (M+H ⁺), 399 (M+Na ⁺) | 2-fluorobenzoyl chloride in anhydrous pyridine |
| 5 | 4-[[5-amino-1-(2,4-difluorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.88 (s, 1H), 7.95 (s, 2H), 7.78-7.58 (m, 4H), 7.48 (s, 2H), 7.35-7.77 (m, 2H), 6.38 (s, 2H); MS (ESI) m/z: 395 (M+H ⁺), 417 (M+Na ⁺) | 2,4-difluoromethylbenzoyl chloride in anhydrous pyridine |
| 6 | 4-[[5-amino-1-[2-fluoro-6-(trifluoromethyl)benzoyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.86 (s, 1H), 8.06 (s, 2H), 7.85 (m, 3H), 7.54 (d, J=8.9 Hz, 2H), 7.40 (d, J= 8.9 Hz, 2H), 7.09 (s, 2H); MS (ESI) m/z: 445 (M+H ⁺), 467 (M+Na ⁺) | 2-fluoro-6-(trifluoromethyl)-benzoyl chloride in THF |
| 7 | 4-[[5-amino-1-(2,6-dichlorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.82 (s, 1H), 7.68-7.45 (m, 9H), 6.35 (s, 2H); (CD ₃ OD) δ 7.60 (d, 2H), 7.55 (m, 3H), 7.38 (d, 2H); MS (ESI) m/z: 428 (M+H ⁺), 450 (M+Na ⁺) | 2,6-dichlorobenzoyl chloride in anhydrous pyridine |
| 8 | 4-[[5-amino-1-(2,4,6-trichlorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.88 (s, 1H), 7.78 (s, 2H), 7.75-7.48 (m, 6H), 6.38 (s, 2H); MS (ESI) m/z: 462 (M+H ⁺), 484 (M+Na ⁺) | 2,4,6-trichlorobenzoyl chloride in anhydrous pyridine |
| 9 | 4-[[5-amino-1-(2-nitrobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, CD ₃ OD) δ 8.28 (d, 2H), 8.95-7.85 (m, 3H), 7.62 (d, 2H), 7.35 (d, 2H); MS (ESI) m/z: 404 (M+H ⁺), 426 (M+Na ⁺) | 2-nitrobenzoyl chloride in anhydrous pyridine |

- 10 4-[[5-amino-1-(2,6-dimethoxybenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 2,6-dimethoxybenzoyl chloride in anhydrous pyridine
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.65 (s, br, 1H), 7.68 (m, 4H), 7.50 (d, 1H), 7.30 (s, br, 2H), 6.72 (d, 1H), 6.68 (dd, 1H), 6.35 (s, br, 2H), 3.92 (s, 3H), 3.85 (s, 3H); MS (ESI) m/z: 419 (M+H⁺), 441 (M+Na⁺)
- 11 4-[[5-amino-1-(2,4,6-trimethylbenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 2,4,6-trimethylbenzoyl chloride in anhydrous pyridine
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.78 (s, 1H), 7.78 (s, 2H), 7.72-7.43 (m, 5H), 7.75-6.78 (m, 3H), 6.35 (s, 2H), 2.38-2.16 (m, 9H); MS (ESI) m/z: 401 (M+H⁺), 423 (M+Na⁺)
- 12 4-[(5-amino-1-benzoyl-1*H*-1,2,4-triazol-3-yl)amino]-benzenesulfonamide Benzoyl chloride in anhydrous pyridine
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.80 (s, 1H), 8.28 (d, 2H), 7.80-7.58 (m, 7H), 7.52 (s, 2H), 6.38 (s, 2H); MS (ESI) m/z: 359 (M+H⁺), 381 (M+Na⁺)
- 14 4-[[5-amino-1-(2-thienylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide Thiophene-2-carboxylic acid mediated by DIC/HOBt (1-hydroxybenzo triazole) in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.92 (s, 1H), 8.40 (dd, 1H), 8.12 (dd, 1H), 7.88 (q, 4H), 7.50 (s, 2H), 7.32 (t, 1H), 6.45 (s, 2H); MS (ESI) m/z: 365 (M+H⁺), 387 (M+Na⁺)
- 15 4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 3-methyl-thiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
m.p. 280 - 284 °C; ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.88 (s, 1H), 8.05 (d, 1H), 7.88 (s, 2H), 7.78 (q, 4H), 7.15 (m, 3H), 2.62 (s, 3H);
(CD₃)₂CO δ 8.92 (s, 1H), 7.98 (d, 1H), 7.90 (q, 4H), 7.45 (s, 2H), 7.15 (d, 1H), 6.42 (s, 2H), 2.68 (s, 3H);
¹³C NMR (300 MHz, (CD₃)₂SO) δ 160.6, 157.9, 157.4, 157.2, 150.9, 143.9, 136.0, 135.5, 131.8, 127.3, 124.3, 116.3, 18.1; MS (ESI) m/z: 379 (M+H⁺), 401 (M+Na⁺)
- 16 4-[[5-amino-1-[(3-fluoro-2-thienyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 3-fluorothiophene-2-carboxylic acid (prepared according to E. C. Taylor and P. Zhou, *Org. Prep. Proced. Int.*, **1997**, 29, 221) mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.92 (s, br, 1H), 8.18 (t, 1H), 7.92 (s, br, 2H), 7.78 (q, 4H), 7.25 (d, 1H), 7.18 (s, br, 2H); MS (ESI) m/z: 383 (M+H⁺), 405 (M+Na⁺)

- | | | |
|----|---|---|
| 17 | 4-[[5-amino-1-[(3-chloro-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.92 (s, br, 1H), 8.25 (d, 1H), 7.95 (s, br, 2H), 7.78 (q, 4H), 7.32 (d, 1H), 7.18 (s, br, 2H); MS (ESI) m/z: 399 (M+H ⁺), 421 (M+Na ⁺) | 3-chlorothiophene-2-carboxylic acid mediated by EDCI/HOBt in anhydrous DMF |
| 18 | 4-[[5-amino-1-[(3-ethoxy-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.85 (s, br, 1H), 8.08 (d, 1H), 7.85-7.75 (m, 6H), 7.28 (d, 1H), 7.15 (s, br, 2H); MS (ESI) m/z: 409 (M+H ⁺), 431 (M+Na ⁺) | 3-ethoxythiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF |
| 19 | <i>N</i> -[2-[[5-amino-3-[[4-(aminosulfonyl)phenyl]amino]-1 <i>H</i> -1,2,4-triazol-1-yl]carbonyl]-3-thienyl]-acetamide

¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 11.0 (s, br, 1H), 9.92 (s, br, 1H), 8.18 (q, 2H), 7.85 (s, br, 2H), 7.78 (q, 4H), 7.15 (s, br, 2H), 2.20 (s, 3H); MS (ESI) m/z: 421 (M+H ⁺), 444 (M+Na ⁺) | 3-(acetylamino)-thiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF |
| 20 | 4-[[5-amino-1-[(5-methyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.92 (s, br, 1H), 8.15 (d, 1H), 7.85 (s, br, 2H), 7.78 (q, 4H), 7.20 (s, br, 2H), 7.08 (d, 1H), 2.62 (s, 3H); MS (ESI) m/z: 379 (M+H ⁺) | 5-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF |
| 21 | 4-[[5-amino-1-[(5-bromo-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.98 (s, br, 1H), 8.05 (d, 1H), 7.95 (s, br, 2H), 7.78 (q, 4H), 7.48 (d, 1H), 7.20 (s, br, 2H); MS (ESI) m/z: 444 (M+H ⁺) | 5-bromothiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF |
| 22 | 4-[[1-[(5-acetyl-2-thienyl)carbonyl]-5-amino-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 10.02 (s, br, 1H), 8.28 (d, 1H), 8.02 (d, 1H), 7.95 (s, br, 2H), 7.75 (q, 4H), 7.20 (s, br, 2H), 2.65 (s, 3H); MS (ESI) m/z: 407 (M+H ⁺), 429 (M+Na ⁺) | 5-acetylthiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF |
| 25 | 4-[[5-amino-1-(2-furanylcarbonyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonamide

¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.87 (s, 1H), 8.20 (d, 1H), 8.02 (dd, 1H), 7.85 (q, 4H), 7.48 (s, 2H), 6.88 (dd, 1H), 6.42 (s, 2H); MS (ESI) m/z: 349 (M+H ⁺), 371 (M+Na ⁺) | 2-furoyl chloride in anhydrous pyridine |

- 26 4-[[5-amino-1-(5-isoxazolylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.95 (s, br, 1H), 8.92 (d, 1H), 8.00 (s, br, 2H), 7.78 (d, 2H), 7.68 (m, 3H), 7.15 (s, br, 2H); MS (ESI) *m/z*: 350 (M+H⁺), 372 (M+Na⁺)
isoxazole-5-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 27 4-[[5-amino-1-(2-pyridinylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.75 (s, 1H), 8.72 (d, 1H), 8.00 (m, 2H), 7.90 (s, br, 2H), 7.68-7.48 (m, 5H), 7.10 (s, br, 2H); MS (ESI) *m/z*: 360 (M+H⁺), 382, (M+Na⁺)
picolic acid mediated by DIC/HOBt in anhydrous DMF
- 28 4-[[5-amino-1-(3-pyridinylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.82 (s, 1H), 9.22 (d, 1H), 8.78 (dd, 1H), 8.45 (dd, 1H), 7.92 (s, br, 2H), 7.62 (q, 4H), 7.15 (s, br, 2H); MS (ESI) *m/z*: 360 (M+H⁺), 382, (M+Na⁺)
nicotinic acid mediated by DIC/HOBt in anhydrous DMF
- 29 4-[[5-amino-1-(4-pyridinylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.80 (s, 1H), 8.82 (d, 2H), 8.00-7.90 (m, 4H), 7.60 (q, 4H), 7.12 (s, br, 2H); MS (ESI) *m/z*: 360 (M+H⁺), 382, (M+Na⁺)
isonicotinic acid mediated by DIC/HOBt in anhydrous DMF
- 30 4-[[5-amino-1-(3-thienylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 9.08 (d, 1H), 8.85 (s, br, 1H), 7.98 (dd, 1H), 7.82 (q, 4H), 7.62 (dd, 1H), 7.48 (s, br, 1H), 6.45 (s, br, 2H); MS (ESI) *m/z*: 365 (M+H⁺), 387 (M+Na⁺)
thiophene-3-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 31 4-[[5-amino-1-(benzo[*b*]thien-2-ylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.95 (s, br, 1H), 8.85 (s, 1H), 8.15 (dd, 2H), 8.02 (s, br, 2H), 7.85 (q, 4H), 7.55 (m, 2H), 7.18 (s, br, 2H); MS (ESI) *m/z*: 415 (M+H⁺)
benzo[*b*]thiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 34 4-[[5-amino-1-[(2,4-dimethyl-5-thiazolyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.88 (s, br, 1H), 7.90 (s, br, 2H), 7.78 (q, 4H), 7.15 (s, br, 2H), 2.78 (s, 6H); MS (ESI) *m/z*: 394 (M+H⁺), 416 (M+Na⁺)
2,4-dimethylthiazole-5-carboxylic acid mediated by DIC/HOBt in anhydrous DMF

- 35 4-[[5-amino-1-[(3-bromo-2-thienyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 3-bromothiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.95 (s, 1H), 8.23 (d, J=5.3, 1H), 7.95 (s, 2H), 7.77 (s, 4H), 7.39 (d, J=5.3, 1H), 7.16 (s, 2H); MS (ESI) m/z: 444.9 (M+H), 466.9 (M+Na⁺)
- 36 4-[[5-amino-1-[(4-methyl-1,2,3-thiadiazol-5-yl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 4-methyl-1,2,3-thiadiazol-5-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 10.07 (s, 1H), 8.09 (s, 2H), 7.86 (d, J=8.8, 2H), 7.72 (d, J=8.9, 2H), 7.21 (s, 2H), 3.02 (s, 3H); MS (ESI) m/z: 381.0 (M+H), 403.0 (M+Na⁺)
- 37 4-[[5-amino-1-(1,2,3-thiadiazol-4-ylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 1,2,3-thiadiazole-4-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 10.18 (s, 1H), 9.93 (s, 1H), 8.05 (s, 2H), 7.76 (d, J=8.8, 2H), 7.63 (d, J=8.8, 2H), 7.16 (s, 2H); MS (ESI) m/z: 367.0 (M+H), 389.0 (M+Na⁺)
- 38 4-[[5-amino-1-(cyclopentylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide cyclopentanecarboxylic acid mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.73 (s, 1H), 7.69 (s, 4H), 7.65 (s, 2H), 7.13 (s, 2H), 1.78 (m, 3H), 1.65 (m, 6H); MS (ESI) m/z: 351.0 (M+H), 373.0 (M+Na⁺)
- 39 4-[[5-amino-1-(cyclohexylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide cyclohexanecarboxylic acid mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.76 (s, 1H), 7.69 (s, 4H), 7.66 (s, 2H), 7.13 (s, 2H), 1.98 (s, 2H), 1.80 (s, 2H), 1.69 (d, 1H), 1.36 (m, 6H); MS (ESI) m/z: 365.0 (M+H), 387.1 (M+Na⁺)
- 40 4-[[5-amino-1-(2-thienylacetyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 2-thiopheneacetic acid mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.80 (s, 1H), 7.73 (d, J=1.2, 4H), 7.69 (s, 2H), 7.45 (dd, J=1.5, 1H), 7.16 (s, 2H), 7.08 (d, J=2.7, 1H), 7.01 (t, J=5.1, 1H), 4.52 (s, 2H); MS (ESI) m/z: 379.0 (M+H), 400.9 (M+Na⁺)
- 42 4-[[5-amino-1-[(2*E*)-1-oxo-3-(2-thienyl)-2-propenyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide 3-(2-thienyl)acrylic acid mediated by DIC/HOBt in anhydrous DMF
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.82 (s, 1H), 7.92 (d, J=8.3, 1H), 7.72 (s, 4H), 7.35 (d, J=15.8, 2H), 7.26 (d, J=19.5, 3H), 7.15 (s, 2H), 6.26 (s, 1H); MS (ESI) m/z: 391.0 (M+H), 412.9 (M+Na⁺)

- 43 4-[[5-amino-1-[(2,6-difluorophenyl)acetyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.81 (s, 1H), 7.69 (s, 6H), 7.44 (t, J=16.6, 1H), 7.16 (s, 3H), 4.37 (s, 2H); MS (ESI) m/z: 409.0 (M+H), 431.0 (M+Na⁺)
 2,6-difluorophenyl acetic acid mediated by DIC/HOBt in anhydrous DMF
- 44 4-[[5-amino-1-[(2*E*)-3-(2,6-difluorophenyl)-1-oxo-2-propenyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.86 (s, 1H), 7.85 (d, J=4.7, 2H), 7.71 (s, 4H), 7.31 (m, 4H), 7.16 (s, 2H), 6.31 (s, 1H); MS (ESI) m/z: 421.0 (M+H), 442.9 (M+Na⁺)
 2,6-difluoro cinnamic acid mediated by DIC/HOBt in anhydrous DMF
- 45 4-[[5-amino-1-(cycloheptylcarbonyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.75 (s, 1H), 7.69 (s, 4H), 7.66 (s, 2H), 7.12 (s, 2H), 2.00 (d, J=11.7, 2H), 1.77 (d, J=10.5, 2H), 1.40 (m, 3H), 1.07 (m, 2H), 0.91 (d, J=6.4, 4H); MS (ESI) m/z: 254, 379.0 (M+H), 401.0 (M+Na⁺)
 cycloheptanecarboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 46 4-[[5-amino-1-[(4-methylcyclohexyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.75 (s, 1H), 7.69 (s, 4H), 7.66 (s, 2H), 7.12 (s, 2H), 2.00 (d, J=11.7, 2H), 1.77 (d, J=10.5, 2H), 1.40 (m, 3H), 1.07 (m, 2H), 0.91 (d, J=6.4, 4H); MS (ESI) m/z: 254, 379.0 (M+H), 401.0 (M+Na⁺)
 trans-4-methyl-1-cyclohexanecarboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 47 4-[[5-amino-1-[(2-methylcyclohexyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.75 (s, 1H), 7.68 (s, 4H), 7.66 (s, 2H), 7.13 (s, 2H), 1.55 (m, 9H), 0.85 (d, J=6.0, 4H); MS (ESI) m/z: 254, 379.0 (M+H), 401.0 (M+Na⁺)
 2-methyl-1-cyclohexanecarboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 48 4-[[5-amino-1-[(4-butylcyclohexyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.75 (s, 1H), 7.68 (s, 4H), 7.66 (s, 2H), 7.12 (s, 2H), 2.02 (d, J=11.3, 2H), 1.82 (d, J=9.9, 2H), 1.40 (d, J=11.3, 2H), 1.25 (s, 7H), 1.02 (m, 4H), 0.87 (s, 4H). MS (ESI) M/Z: 254, 435.1 (M+H), 457.1 (M+Na⁺)
 trans-4-butyl-1-cyclohexanecarboxylic acid mediated by DIC/HOBt in anhydrous DMF

- 49 4-[[5-amino-1-[[5-(2-pyridinyl)-2-thienyl]carbonyl]-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.98 (s, 1H), 8.65 (d, 1H), 8.25 (d, 1H), 8.08 (d, 1H), 8.02 - 7.75 (m, 8H), 7.42 (dd, 1H), 7.20 (s, 2H). MS (ESI) m/z: 442 (M+H⁺), 464 (M+Na⁺)
 5-(2-pyridyl)-thiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 50 4-[[5-amino-1-[[3-(1H-pyrrol-1-yl)-2-thienyl]carbonyl]-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.85 (s, 1H), 8.18 (d, 1H), 7.85 - 7.70 (m, 6H), 7.32 (d, 1H), 7.18 (s, 2H), 7.12 (t, 2H), 6.20 (t, 2H). MS (ESI) m/z: 430 (M+H⁺)
 3-(1H-pyrrol-1-yl)-thiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 51 4-[[5-amino-1-[[5-(1,1-dimethylethyl)-2-thienyl]carbonyl]-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.95 (s, 1H), 8.25 (d, 1H), 7.95 (d, 2H), 7.85 (d, 2H), 7.50 (s, 2H), 7.18 (d, 1H), 6.48 (s, 2H), 1.55 (s, 9H). MS (ESI) m/z: 421 (M+H⁺), 443 (M+Na⁺)
 5-*tert*-butylthiophene-2-carboxylic acid mediated by DIC/HOBt in anhydrous DMF
- 52 3-[5-[[5-amino-3-[[4-(aminosulfonyl)phenyl]amino]-1H-1,2,4-triazol-1-yl]carbonyl]-2-thienyl]-(2E)-2-propenoic acid-1,1-dimethylethyl ester
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.95 (s, 1H), 8.22 (d, 1H), 7.95 (s, 2H), 7.82-7.68 (m, 6H), 7.15 (s, 2H), 6.52 (d, 1H), 1.52 (s, 9H). MS (ESI) m/z: 491 (M+H⁺), 513 (M+Na⁺)
 5-(2-*tert*-butoxycarbonyl-vinyl)-thiophene-2-carboxylic acid (intermediate) ¹H NMR (300 MHz, (CD₃)₂CO) δ 7.80-7.0 (m, 2H), 7.48 (d, 1H), 7.32 (d, 1H), 1.50 (s, 9H); MS (ESI) m/z: 253 (M-H⁺), 209 (M-H⁺-CO₂)
 5-(2-*tert*-butoxycarbonyl-vinyl)-thiophene-2-carboxylic acid (prepared by Heck reaction of 5-bromothiophene-2-carboxylic acid and *t*-butyl acrylate) mediated by DIC/HOBt in anhydrous DMF
- 53 4-[[5-amino-1-[[5-(phenylethynyl)-2-thienyl]carbonyl]-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.98 (s, 1H), 8.20 (d, 1H), 7.95 (s, 2H), 7.78 (m, 4H), 7.62 (m, 2H), 7.60 (d, 1H), 7.45 (m, 3H), 7.18 (s, 2H). MS (ESI) m/z: 465 (M+H⁺), 487 (M+Na⁺)
 5-phenylethynyl-thiophene-2-carboxylic acid (intermediate) prepared by oxidation of 5-phenylethynyl-thiophene-2-carboxaldehyde, mediated by DIC/HOBt in anhydrous DMF

- 54 4-[[5-amino-1-(2,6-difluoro-3-nitrobenzoyl)-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.90 (s, 1H), 8.55 (m, 1H), 7.75-7.50 (m, 7H), 6.25 (s, 2H); MS (ESI) m/z: 440 (M+H⁺), 462 (M+Na⁺)
 2,6-difluoro-3-nitro-benzoic acid mediated by DIC/HOBt in anhydrous DMF
- 55 4-[[5-amino-1-(3-amino-2,6-difluorobenzoyl)-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃OD) δ 7.68 (d, 2H), 7.45 (d, 2H), 6.95 (m, 1H), 6.85 (m, 1H); MS (ESI) m/z: 410 (M+H⁺), 432 (M+Na⁺)
 catalytic hydrogenation of compound 54 in methanol by catalysis of 10% palladium on charcoal
- 56 4-[[5-amino-1-(2,6-dimethylbenzoyl)-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.75 (s, 1H), 7.65-7.28 (m, 7H), 7.15 (d, 2H), 6.32 (s, 2H), 2.25 (s, 6H); MS (ESI) m/z: 387 (M+H⁺), 409 (M+Na⁺)
 2,6-dimethylbenzoic acid mediated by DIC/HOBt in anhydrous DMF
- 57 4-[[5-amino-1-(2-methylbenzoyl)-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.75 (s, 1H), 7.72-7.25 (m, 10H), 6.35 (s, 2H), 2.45 (s, 3H); MS (ESI) m/z: 373 (M+H⁺), 395 (M+Na⁺)
 2-methylbenzoyl chloride in anhydrous pyridine
- 66 5-amino-3-[[4-(aminosulfonyl)phenyl]amino]-N-(2,6-difluorophenyl)-1H-1,2,4-triazole-1-carbothioamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 10.40 (s, 1H), 8.90 (s, 1H), 8.15 (s, 2H), 7.85 (d, 2H), 7.75 (d, 2H), 7.40 (m, 1H), 7.15 (m, 2H), 6.35 (s, 2H), 5.75 (s, 2H); MS (ESI) m/z: 426 (M+H⁺), 448 (M+Na⁺)
 2,6-difluorophenyl isothiocyanate in anhydrous pyridine
- 67 5-amino-3-[[4-(aminosulfonyl)phenyl]amino]-N-(2,6-difluorophenyl)-1H-1,2,4-triazole-1-carboxamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 9.15 (s, 1H), 8.80 (s, 1H), 7.80 (d, 2H), 7.70 (d, 2H), 7.42 (m, 1H), 7.15 (m, 2H), 7.00 (s, 2H), 6.35 (s, 2H); MS (ESI) m/z: 410 (M+H⁺), 432 (M+Na⁺)
 2,6-difluorophenyl isocyanate in anhydrous DMF
- 68 4-[[5-amino-1-[(2,6-difluorophenyl)sulfonyl]-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide
¹H NMR (300 MHz, (CD₃)₂CO) δ 8.80 (s, 1H), 7.85 (m, 1H), 7.75 (d, 2H), 7.65 (d, 2H), 7.30 (t, 2H), 6.95 (s, 2H), 6.35 (s, 2H); MS (ESI) m/z: 431 (M+H⁺), 453 (M+Na⁺)
 2,6-difluorobenzenesulfonyl chloride in anhydrous pyridine

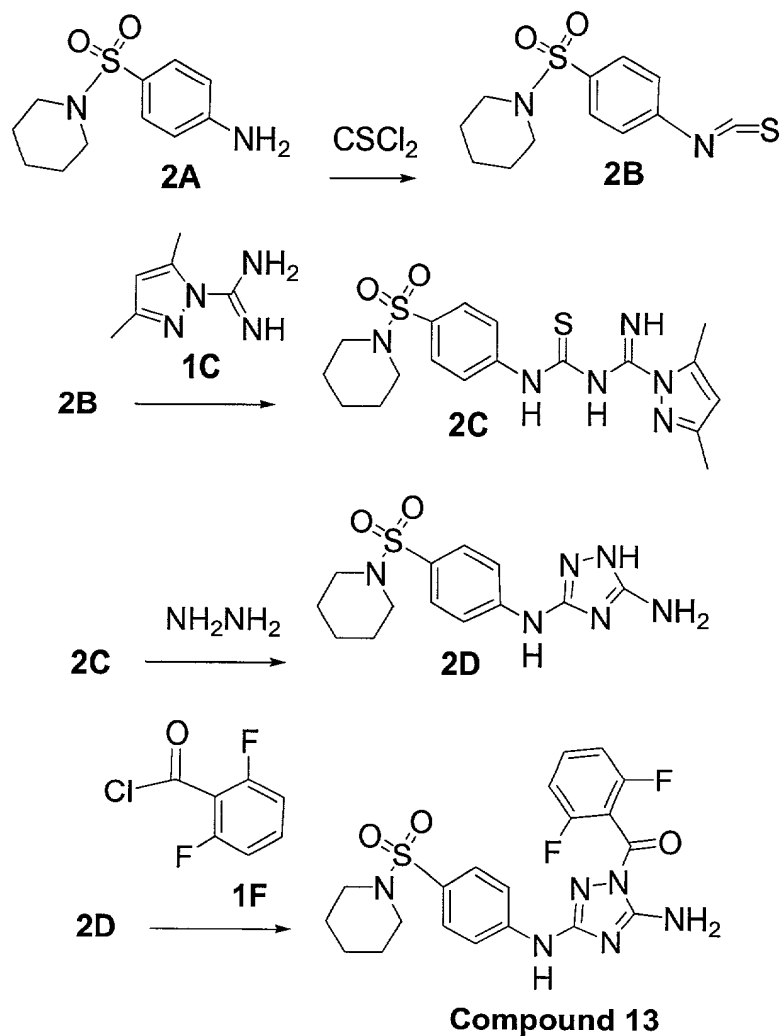
69	4-[[5-amino-1-(2-chloro-6-fluoro-3-methylbenzoyl)-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide ¹ H NMR (300MHz, (CD ₃) ₂ SO) δ 9.85 (s, 1H), 8.05 (s, 2H), 7.64-7.55 (m, 3H), 7.45-7.35 (m, 3H), 7.10 (s, 2H), 2.38 (s, 3H); MS (ESI) m/z: 425 (M+H ⁺), 447 (M+Na ⁺)	2-chloro-6-fluoro-3-methylbenzoyl chloride in anhydrous pyridine
70	4-[[5-amino-1-(2-chloro-6-fluorobenzoyl)-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide ¹ H NMR (300MHz, (CD ₃) ₂ SO) δ 9.87 (s, 1H), 8.05 (s, 2H), 7.68-7.63 (m, 1H), 7.57-7.50 (m, 3H), 7.48-7.42 (m, 3H), 7.09 (s, 2H); MS (ESI) m/z: 411 (M+H ⁺), 433 (M+Na ⁺)	2-chloro-6-fluoro benzoyl chloride in anhydrous pyridine
78	4-[[5-amino-1-(3-chloro-2,6-difluorobenzoyl)-1H-1,2,4-triazol-3-yl]amino]-benzenesulfonamide ¹ H NMR (300MHz, (CD ₃) ₂ SO) δ 9.89 (s, 1H), 8.07 (s, 2H), 8.00-7.92 (m, 1H), 7.59 (d, 2H), 7.49-7.44 (m, 3H), 7.12 (s, 2H); MS (ESI) m/z: 429 (M+H ⁺)	3-chloro-2,6-difluorobenzoic acid, mediated by DIC/HOBt in anhydrous DMF
122	4-[[3-amino-1-(2,6-difluorobenzoyl)-1H-1,2,4-triazol-5-yl]amino]-benzenesulfonamide (minor regioisomer of Cpd 1) ¹ H NMR (300 MHz, CD ₃ CN) δ 9.90 (s, 1H), 7.90 (q, 4H), 7.60 (m, 1H), 7.15 (t, 2H), 5.62 (s, 2H), 4.85 (s, 2H); MS (ESI) m/z: 395 (M+H ⁺), 417 (M+Na ⁺)	2,6-difluorobenzoyl chloride in anhydrous pyridine
123	4-[[3-amino-1-(2,6-difluoro-3-methylbenzoyl)-1H-1,2,4-triazol-5-yl]amino]-benzenesulfonamide (minor regioisomer of Cpd 2) ¹ H NMR (300 MHz, ((CD ₃) ₂ SO) δ 10.0 (s, 1H), 8.00 (d, 2H), 7.78 (d, 2H), 7.50 (m, 1H), 7.20 (s, 2H), 7.15 (t, 2H), 6.25 (s, 2H), 2.28 (s, 3H); MS (ESI) m/z: 409 (M+H ⁺), 431 (M+Na ⁺)	2,6-difluorobenzoyl chloride in anhydrous pyridine
128	3-amino-5-[[4-(aminosulfonyl)phenyl]amino]-N-(2,6-difluorophenyl)-1H-1,2,4-triazole-1-carbothioamide (minor regioisomer of Cpd 66) ¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 12.10 (s, 1H), 10.28 (s, 1H), 7.85 (m, 4H), 7.45 (m, 1H), 7.20 (m, 2H), 6.45 (s, 2H), 5.75 (s, 2H); MS (ESI) m/z: 426 (M+H ⁺), 448 (M+Na ⁺)	---

Example 2

1-(2,6-difluorobenzoyl)-N²-[4-(1-piperidinylsulfonyl)phenyl]-1H-1,2,4-triazole-3,5-diamine (Cpd 13)

- 5 Using the procedure for Example 1, 1-amidino-3,5-dimethylpyrazole nitrate Compound 1C was reacted with 1-(4-isothiocyanatophenylsulfonyl)piperidine Compound 2B to

produce Compound **2C**. ^1H NMR (300 MHz, CD_3CN) δ 10.75 (s, br, 1H), 8.40 (s, br, 1H), 7.95 (s, br, 1H), 7.55 (q, 4H), 5.95 (s, 1H), 3.00 (m, 4H), 2.25 (s, 6H), 1.68 (m, 4H), 1.45 (m, 2H); MS (ESI) m/z : 421 ($\text{M}+\text{H}^+$). Compound **2C** was then reacted with hydrazine to produce Compound **2D**. ^1H NMR (300 MHz, CD_3CN) δ 10.75 (s, br, 1H), 7.65 (s, br, 1H), 7.55 (q, 4H), 5.85 (s, br, 2H), 2.82 (m, 4H), 1.55 (m, 4H), 1.32 (m, 2H); MS (ESI) m/z : 323 ($\text{M}+\text{H}^+$). Compound **2D** was acylated with 2,6-difluoro-3-methylbenzoyl chloride Compound **1F** in anhydrous pyridine to produce Compound **13** (85% yield). ^1H NMR (300 MHz, CDCl_3) δ 7.60-7.50 (m, 3H), 7.42 (d, 2H), 7.18 (t, 2H), 6.98 (s, br, 1H), 6.55 (s, br, 2H), 2.98 (m, 4H), 1.65 (m, 4H), 1.42 (m, 2H); MS (ESI) m/z : 363 ($\text{M}+\text{H}^+$), 485 ($\text{M}+\text{Na}^+$).



Using the procedure for Example 3, the following compounds were prepared by

15 acylation of the intermediate Compound **2D** using the indicated starting material in

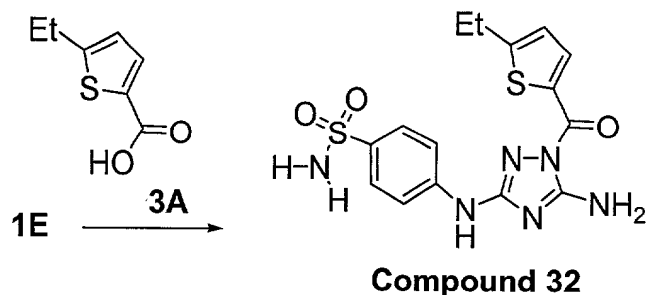
place of Compound **1F** and reagent(s):

Cpd	Name/Data	Starting Mat'l
23	<i>N</i> ³ -[4-(1-piperidinylsulfonyl)phenyl]-1-(2-thienylcarbonyl)-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 10.02 (s, br, 1H), 8.40 (dd, 1H), 8.18 (dd, 1H), 7.92 (s, br, 2H), 7.88 (d, 2H), 7.58 (d, 2H), 7.32 (t, 1H), 2.88 (m, 4H), 1.55 (m, 4H), 1.35 (m, 2H); MS (ESI) <i>m/z</i> : 433 (M+H ⁺), 455 (M+Na ⁺)	thiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
24	1-[(3-methyl-2-thienyl)carbonyl]- <i>N</i> ³ -[4-(1-piperidinylsulfonyl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 10.02 (s, br, 1H), 8.02 (d, 1H), 7.95-7.80 (m, 4H), 7.68 (d, 2H), 7.18 (d, 1H), 2.88 (m, 4H), 2.68 (s, 3H), 1.55 (m, 4H), 1.35 (m, 2H); MS (ESI) <i>m/z</i> : 447 (M+H ⁺), 469 (M+Na ⁺)	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF

Example 3

4-[[5-amino-1-[(5-ethyl-2-thienyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide (Cpd **32**)

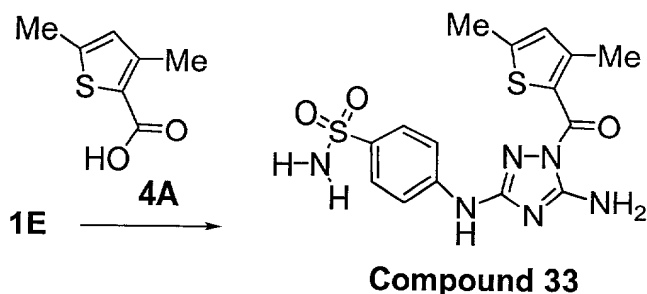
Hydrazine monohydrate (0.97 mL, 1.019 mol) and potassium hydroxide (1.12 g, 20 mmol) were added to a solution of 5-acetyl-thiophene-2-carboxylic acid (1.70 g, 10 mmol) in diethylene glycol (20 mL) and water (1 mL). The reaction mixture was stirred in an oil bath at 110 °C for 16 hrs, cooled to rt, acidified with 2N HCl and then extracted with methylene chloride (4 x 50 mL). Organic layers were combined, dried, concentrated and subjected to chromatography separation on silica gel (eluted with 10 % methanol/methylene chloride) to produce 3-ethylthiophene-2-carboxylic acid Compound **3A** as a pale yellow solid (1.161 g, 74%). ¹H NMR (300 MHz, CD₃OD) δ 7.59 (d, *J* 3.7, 1H), 6.87 (d, *J* 3.7, 1H), 2.88 (q, *J* 7.5, 1H), 1.32 (t, *J* 7.5, 3H); MS (ESI) *m/z*: 155 (M-H⁺). Using the procedure of Example 1, Compound **1E** was acylated with Compound **3A** mediated by DIC/HOBt in anhydrous DMF to produce Compound **32** (59% yield). ¹H NMR (300 MHz, (CD₃)₂CO) δ 8.90 (s, br, 1H), 8.25 (d, 1H), 7.88 (q, 4H), 7.45 (s, br, 2H), 7.10 (d, 1H), 6.45 (s, br, 2H), 3.05 (q, 2H), 1.42 (t, 3H); MS (ESI) *m/z*: 393 (M+H⁺), 415 (M+Na⁺).



Example 4

4-[[5-amino-1-[(3,5-dimethyl-2-thienyl)carbonyl]-1H-1,2,4-triazol-3-yl]amino]-
benzenesulfonamide (Cpd 33)

2.2 equivalents of 2.0 M LDA solution in heptane/THF/ethylbenzene (0.97 mL, 1.019 mol) was added to a solution of 3-methylthiophene-2-carboxylic acid (1.42 g, 10 mmol) in anhydrous THF (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 hr; and then methyl iodide (1.4 mL, 22 mmol) was added. The resulting mixture was stirred at 0 °C for an additional 2 hr, acidified with 2N HCl and extracted with methylene chloride (4 x 50 mL). The organic layers were then combined, concentrated and separated via HPLC to give 3,5-dimethylthiophene-2-carboxylic acid Compound 4A as a white powder. ¹H NMR (300 MHz, CD₃OD) δ 6.72 (s, 1H), 2.43 (s, 3H), 2.46 (s, 3H); MS (ESI) m/z: 155 (M-H⁺). Using the procedure of Example 1, Compound 1E was acylated with Compound 4A mediated by DIC/HOBt in anhydrous DMF to produce Compound 33 (73% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.88 (s, br, 1H), 7.85 (s, br, 2H), 7.78 (q, 4H), 7.18 (s, br, 2H), 6.92 (s, 1H), 2.58 (s, 3H), 2.55 (s, 3H); MS (ESI) m/z: 393 (M+H⁺), 415 (M+Na⁺).



Example 5

4-[[5-amino-1-[2,6-difluoro-3-(1-hydroxyethyl)benzoyl]-1H-1,2,4-triazol-3-yl]amino]-

benzenesulfonamide (Cpd **58**)

2',4'-difluoroacetophenone (5g, 32 mmol) was reacted with sodium borohydride (1.21 g) in THF (20 mL) and methanol (10 mL) for 1 hr. The resultant mixture was evaporated to dryness and partitioned between methylene chloride and water. The organic layer was separated, dried, and evaporated to give 1-(2',4'-difluorophenyl)-ethanol as a colorless oil (4.86 g, 96%). ¹H NMR (300 MHz, CDCl₃) δ 7.48 (m, 1H), 6.85 (m, 1H), 6.75 (m, 1H), 5.15 (q, 1H), 2.0 (s, 1H), 1.5 (d, 3H). 1-(2',4'-difluorophenyl)-ethanol (5.384 g, 34 mmol), t-butyltrimethylsilyl chloride (6.148 g, 40.8 mmol) and imidazole (5.567 g, 81.8 mmol) in DMF (60 mL) were combined and stirred at rt overnight. The resultant mixture was evaporated to dryness in vacuo, and then the residue was partitioned between methylene chloride and water. The organic layer was separated, dried and evaporated to give 1-(2',4'-difluorophenyl)-ethyl t-butyltrimethylsilyl ether as a white solid (6.88 g, 74%). ¹H NMR (300 MHz, CDCl₃) δ 7.45 (q, 1H), 6.75 (m, 1H), 6.62 (m, 1H), 5.05 (q, 1H), 1.32 (d, 3H), 0.88 (s, 9H), 0.05 and 0.01 (each s, each 3H). A 1.6 M solution of n-butyl lithium in hexane (3.75 mL, 6 mmol) was added dropwise to a solution of 1-(2',4'-difluorophenyl)-ethyl t-butyltrimethylsilyl ether (1.362 g, 5 mmol) in THF (60 mL) at -50 °C and was stirred at the same temperature for 3 h. The reaction mixture was poured to dry ice; and then was evaporated to dryness. The residue was partitioned between methylene chloride and water, acidified with acetic acid. The organic layer was separated, dried, and evaporated to give 2,6-difluoro-3-(1-t-butyltrimethylsilyloxyethyl)-benzoic acid Compound **5A** as white solid (1.57 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 7.70 (q, 1H), 7.00 (t, 1H), 6.00 (br, 1H), 5.15 (q, 1H), 1.40 (d, 3H), 0.90 (s, 9H), 0.12 and 0.05 (each s, each 3H).

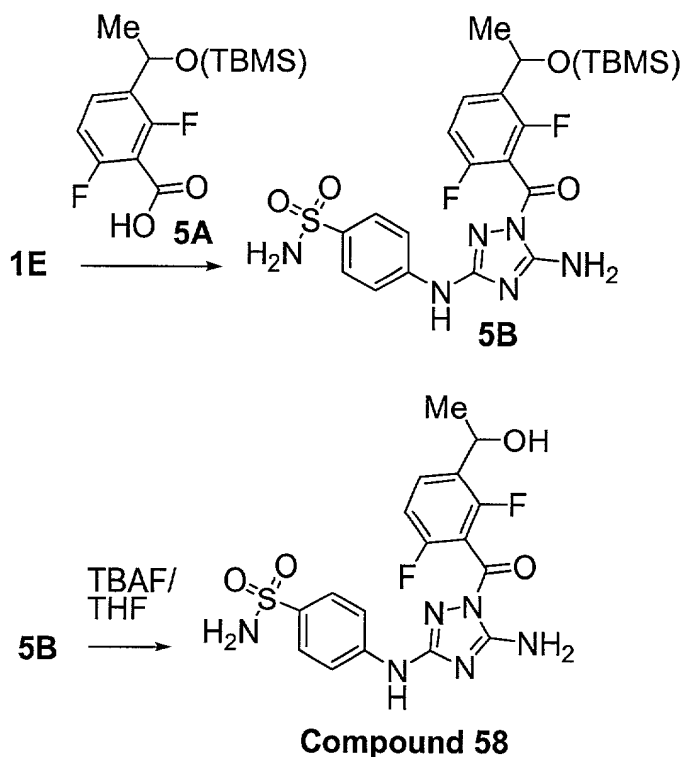
Using the procedure of Example 1, Compound **1E** was acylated with Compound **5A** mediated by DIC/HOBt in anhydrous DMF to provide 4-[[5-amino-1-(2,6-difluoro-3-(1-t-butyltrimethylsilyloxyethyl)-benzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide Compound **5B** (46% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.72 (m, 3H), 7.38 (d, 2H), 7.02 (t, 1H), 6.80 (s, 1H), 6.45 (s, 2H), 5.15 (q, 1H), 4.68 (s, 2H), 1.15 (d, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H); MS (ESI) *m/z*: 553 (M+H⁺), 575 (M+Na⁺). 4-[[5-amino-2-(2,6-difluoro-3-(1-t-butyltrimethylsilyloxyethyl)-benzoyl)-2*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide (a minor regioisomer) was also

isolated from the reaction mixture (192 mg, 34%). ^1H NMR (300 MHz, CDCl_3) δ 10.00 (s, 1H), 7.92 (d, 2H), 7.82 (d, 2H), 7.70 (q, 1H), 7.02 (t, 1H), 5.18 (q, 1H), 4.82 (s, 2H), 4.32 (s, 2H), 1.42 (d, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H); MS (ESI) m/z : 553 ($\text{M}+\text{H}^+$), 575 ($\text{M}+\text{Na}^+$).

5

0.7 mL of 1.0 M TBAF solution in THF was added to a solution of 4-[[5-amino-1-(2,6-difluoro-3-(1-*t*-butyltrimethylsilyloxyethyl)-benzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonamide Compound **5B** (193 mg, 0.35 mol) in THF (10 mL). The reaction solution was stirred at rt for 1 hr and evaporated to dryness. The resultant residue was then subjected to column chromatography on silica gel with 20% methanol/methylene chloride to give the product Compound **58** as a white foam (90 mg, 59%). ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.85 (s, 1H), 8.00 (s, 2H), 7.75 (m, 1H), 7.55 (m, 2H), 7.45 (m, 2H), 7.30 (t, 1H), 7.10 (s, 2H), 6.80 (s, 1H), 5.55 (d, 1H), 5.00 (m, 1H), 1.38 (d, 3H); MS (ESI) m/z : 421 ($\text{M}+\text{H}^+-\text{H}_2\text{O}$), 439 ($\text{M}+\text{H}^+$), 461 ($\text{M}+\text{Na}^+$).

15

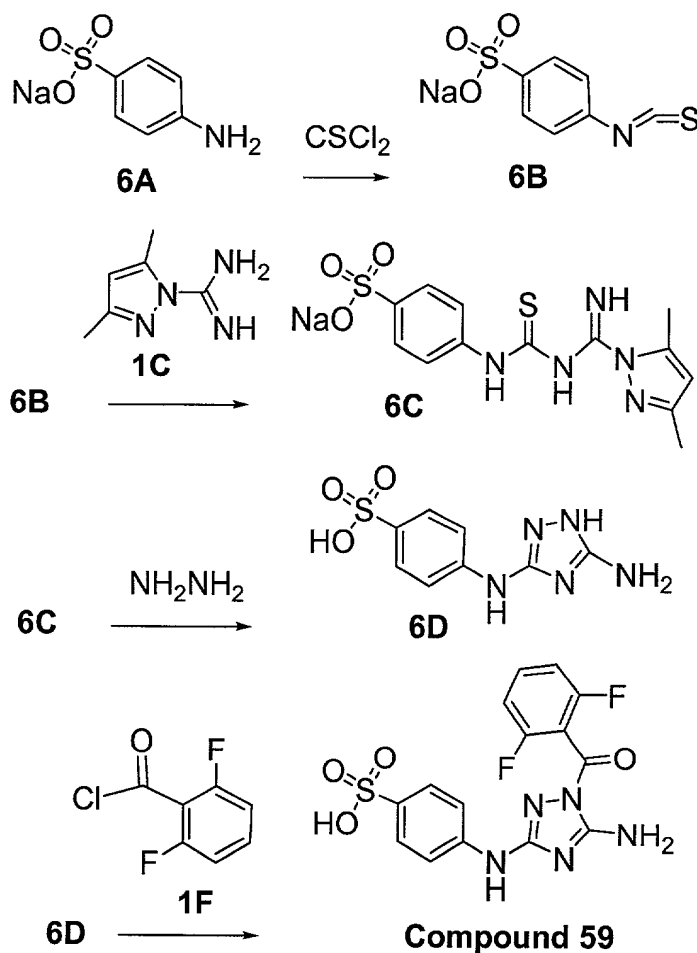


Example 6

4-[[5-amino-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-benzenesulfonic acid
(Cpd **59**)

20

The sodium salt of 4-sulfophenyl isothiocyanate Compound **6B**, (prepared using the procedure of Example 1) was reacted with 1-amidino-3,5-dimethylpyrazole nitrate Compound **1C** to produce Compound **6C** which was reacted with hydrazine to produce Compound **6D**. ¹H NMR (300 MHz, (CD₃)₂SO) δ 11.1 (s, 1H), 8.75 (s, 1H), 7.3 (m, 4H), 5.85 (s, 2H); MS (ESI) m/z: 256 (M+H⁺). Using the procedure of Example 1, Compound **6D** was acylated with 2,6-difluorobenzoyl chloride Compound **1F** in anhydrous pyridine to produce compound **59** (4% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.35 (s, 1H), 7.95 (s, 2H), 7.82 (m, 2H), 7.45-7.25 (m, 5H); MS (ESI) m/z: 396 (M+H⁺).



Using the procedure for Example 6, the following compounds were prepared by acylation of the intermediate Compound **6D** using the indicated starting material in place of Compound **1F** and reagent(s):

Cpd	Name/Data	Starting Mat'l
-----	-----------	----------------

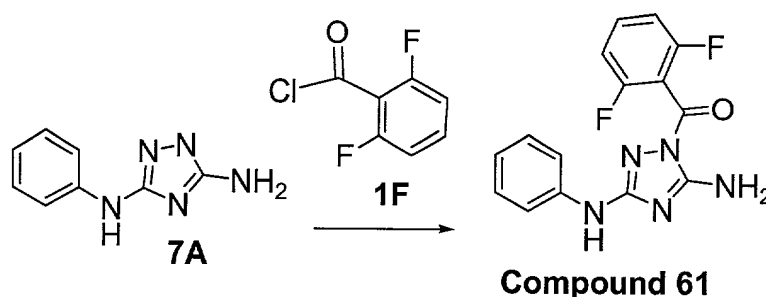
60	4-[[5-amino-1-(2,6-difluoro-3-methylbenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]-benzenesulfonic acid	2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine
	¹ H NMR (300 MHz, CD ₃ OD) δ 7.62 (d, 2H), 7.50 (m, 1H), 7.38 (d, 2H), 7.05 (m, 1H), 2.30 (s, 3H); MS (ESI) m/z: 410 (M+H ⁺)	

Example 7

1-(2,6-Difluorobenzoyl)-*N*³-phenyl-1*H*-1,2,4-triazole-3,5-diamine (Cpd 61)

3-Anilino-5-amino-1,2,4-triazole Compound 7A (prepared using the procedure of

- 5 Example 1) was acylated with 2,6-difluorobenzoyl chloride Compound 1F in anhydrous pyridine to produce Compound 61 as a white solid (61% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.80 (s, 1H), 7.45 (m, 1H), 7.30-7.15 (m, 4H), 7.05-6.85 (m, 5H), 6.70 (s, 2H); MS (ESI) m/z: 316 (M+H⁺), 338 (M+Na⁺).



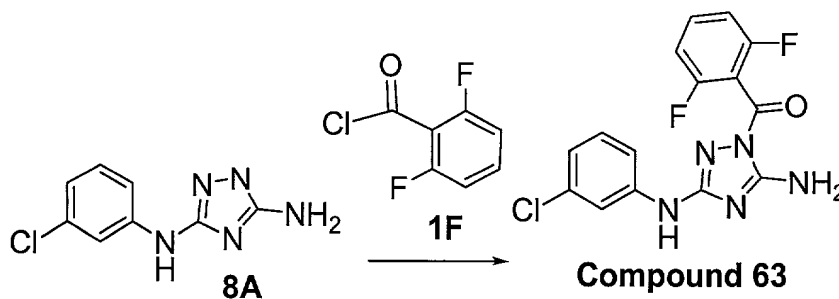
Using the procedure for Example 7, the following compounds were prepared by acylation of Compound 7A using the indicated starting material in place of Compound 1F and reagent(s):

Cpd	Name/Data	Starting Mat'l
62	1-benzoyl- <i>N</i> ³ -phenyl-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, CDCl ₃) δ 8.30 (s, 2H), 7.65-7.40 (m, 5H), 7.28 (d, 2H), 7.00 (t, 1H), 6.80 (s, 1H), 6.70 (s, 2H); MS (ESI) m/z: 280 (M+H ⁺), 302 (M+Na ⁺)	benzoyl chloride in anhydrous pyridine
65	5-amino- <i>N</i> -phenyl-3-(phenylamino)-1 <i>H</i> -1,2,4-triazole-1-carboxamide ¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 9.20 (s, 1H), 8.20 (s, 1H), 7.70 (m, 4H), 7.35 (t, 2H), 7.25 (t, 2H), 7.15 (t, 1H), 7.98 (s, 2H), 6.88 (t, 1H); MS (ESI) m/z: 295 (M+H ⁺), 317 (M+Na ⁺)	phenyl isocyanate in anhydrous DMF

- 124 1-(2,6-difluorobenzoyl)-*N*⁵-phenyl-1*H*-1,2,4-triazole-3,5-diamine ---
 (minor regioisomer of Cpd **61**) ¹H NMR (300 MHz, CDCl₃) δ 9.80 (s, 1H), 7.65 (d, 2H), 7.60-7.32 (m, 3H), 7.25-7.00 (m, 3H), 4.40 (s, 2H); MS (ESI) *m/z*: 316 (M+H⁺), 338 (M+Na⁺)
- 125 1-benzoyl-*N*⁵-phenyl-1*H*-1,2,4-triazole-3,5-diamine ---
 (minor regioisomer of Cpd **62**) ¹H NMR (300 MHz, CDCl₃) δ 10.20 (s, 1H), 8.18 (d, 2H), 7.72-7.30 (m, 7H), 7.15 (t, 1H), 4.30 (s, 2H); MS (ESI) *m/z*: 280 (M+H⁺), 302 (M+Na⁺)

Example 8

- N*³-(3-chlorophenyl)-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazole-3,5-diamine (Cpd **63**)
 3-(3-Chloroanilino)-5-amino-1,2,4-triazole Compound **8A** (prepared using the
 5 procedure of Example 1) was acylated with 2,6-difluorobenzoyl chloride Compound **1F**
 in anhydrous pyridine to produce Compound **63** as a pale yellow solid (66% yield). ¹H
 NMR (300 MHz, CDCl₃) δ 7.6-7.50 (m, 2H), 7.15-6.80 (m, 6H), 6.60 (s, 2H); MS
 (ESI) *m/z*: 350 (M+H⁺), 372 (M+Na⁺).



10

Using the procedure for Example 8, the following compounds were prepared by acylation of the intermediate Compound **8A** using the indicated starting material in place of Compound **1F** and reagent(s):

Cpd	Name/Data	Starting Mat'l
64	1-benzoyl- <i>N</i> ³ -(3-chlorophenyl)-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ CO) δ 8.58 (s, 1H), 8.30 (d, 2H), 8.00 (m, 1H), 7.75-7.25 (m, 6H), 6.90 (d, 1H); MS (ESI) <i>m/z</i> : 314 (M+H ⁺), 336 (M+Na ⁺)	benzoyl chloride in anhydrous pyridine

- 126 *N*⁵-(3-chlorophenyl)-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazole-3,5-diamine

(minor regioisomer of Cpd 63) ¹H NMR (300 MHz, CDCl₃) δ 9.90 (s, 1H), 7.90 (s, 1H), 7.58-6.95 (m, 7H), 4.35 (s, 2H); MS (ESI) *m/z*: 350 (M+H⁺), 472 (M+Na⁺)

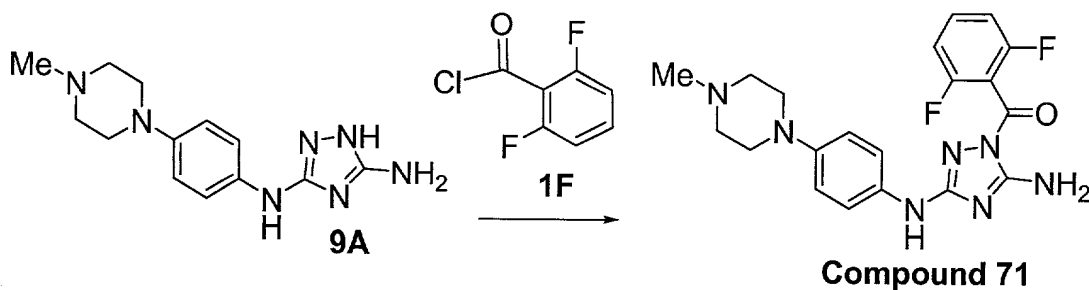
- 127 1-benzoyl-*N*⁵-(3-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine

(minor regioisomer of Cpd 64) ¹H NMR (300 MHz, (CD₃)₂CO) δ 10.30 (s, 1H), 8.20 (d, 2H), 8.15 (m, 1H), 7.70-7.60 (m, 2H), 7.55 (t, 2H), 7.35 (t, 1H), 7.10 (d, 1H), 5.60 (s, 2H); MS (ESI) *m/z*: 314 (M+H⁺), 336 (M+Na⁺)

Example 9

1-(2,6-difluorobenzoyl)-*N*⁵-[4-(4-methyl-1-piperazinyl)phenyl]-1*H*-1,2,4-triazole-3,5-diamine (Cpd 71)

- 5 4-(4-Methylpiperazino)-phenyl isothiocyanate was reacted with 1 equivalent of 3,5-dimethylpyrazole-1-carboxamide nitrate and 1.1 equivalents of potassium *t*-butoxide in DMSO at 55 °C for 4 hours. 10 equivalents of hydrazine were added and stirred at 55 °C for 4 hrs. Subsequent concentration, dissolution in methanol, filtering of impurities and concentration gave 3-(4-methylpiperazino)-anilino-5-amino-1,2,4-triazole
- 10 Compound 9A (87% yield). ¹H NMR (400MHz, (CD₃)₂SO) δ 9.05 (s, 1H), 8.60 (s, 1H), 7.35 (d, 2H), 6.77 (d, 2H), 5.70 (s, 2H), 2.97 (m, 4H), 2.48 (m, 4H), 2.23 (s, 3H); MS (ESI) *m/z*: 274 (M+H⁺). 3-(4-methylpiperazino)-anilino-5-amino-1,2,4-triazole
- Compound 9A was acylated with 2,6-difluoro benzoyl chloride Compound 1F in anhydrous pyridine to produce compound 71 (30% yield). ¹H NMR (300MHz,
- 15 (CD₃)₂SO) δ 9.07 (s, 1H), 7.88 (s, 1H), 7.72-7.66 (m, 1H), 7.32 (t, 1H), 7.25-7.17 (m, 2H), 6.97-6.92 (m, 1H), 6.71 (d, 1H), 3.39-3.35 (m, 2H), 3.17 (s, 3H), 3.00-2.97 (m, 4H), 2.51-2.46 (m, 4H); MS (ESI) *m/z*: 414 (M+H⁺).



Using the procedure for Example 9, the following compounds were prepared by acylation of the intermediate Compound 9A using the indicated starting material in place of Compound 1F and reagent(s):

Cpd	Name/Data	Starting Mat'l
72	1-(2,6-difluoro-3-methylbenzoyl)- <i>N</i> ³ -[4-(4-methyl-1-piperazinyl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300MHz, (CD ₃) ₂ SO) δ 9.05(s, 1H), 7.87 (s, 1H), 7.59-7.51 (m, 1H), 7.24-7.18 (m, 2H), 6.72 (d, 2H), 3.35 (s, 2H), 2.99-2.96 (m, 4H), 2.45-2.42 (m, 4H), 2.28 (s, 3H); MS (ESI) m/z: 428 (M+H ⁺)	2,6-difluoro-3-methyl benzoyl chloride in anhydrous pyridine
73	<i>N</i> ³ -[4-(4-methyl-1-piperazinyl)phenyl]-1-[(3-methyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300MHz, (CD ₃) ₂ SO) δ 9.13 (s, 1H), 7.77 (s, 1H), 7.58-7.55 (m, 2H), 7.38-7.26 (m, 1H), 6.92 (d, 2H), 3.17 (s, 3H), 3.09-3.07 (m, 4H), 2.62 (s, 4H), 2.35 (s, 3H); MS (ESI) m/z: 398 (M+H ⁺)	3-methyl-2-thiophene carboxylic acid, mediated by DIC/HOBt in anhydrous DMF
74	1-[(3,5-dimethyl-2-thienyl)carbonyl]- <i>N</i> ³ -[4-(4-methyl-1-piperazinyl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300MHz, (CD ₃) ₂ SO) δ 9.11 (s, 1H), 7.73 (s, 2H), 7.59-7.54 (m, 2H), 7.38-7.26 (m, 1H), 6.94 (d, 2H), 3.16-3.13 (m, 4H), 2.80-2.78 (m, 4H), 2.56 (s, 3H), 2.53 (s, 3H), 2.46 (s, 3H); MS (ESI) m/z: 412 (M+H ⁺)	3,5-dimethyl-2-thiophene carboxylic acid, mediated by DIC/HOBt in anhydrous DMF
75	1-[(5-ethyl-2-thienyl)carbonyl]- <i>N</i> ³ -[4-(4-methyl-1-piperazinyl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300MHz, (CD ₃) ₂ SO) δ 9.17 (s, 1H), 7.78 (s, 1H), 7.51 (d, 2H), 7.35-7.24 (m, 3H), 7.08 (d, 2H), 3.14-3.12 (m, 4H), 2.96 (q, 2H), 2.76-2.73 (m, 4H), 2.43 (s, 3H), 1.34 (t, 3H); MS (ESI) m/z: 412 (M+H ⁺)	5-ethyl-2-thiophene carboxylic acid, mediated by DIC/HOBt in anhydrous DMF

5

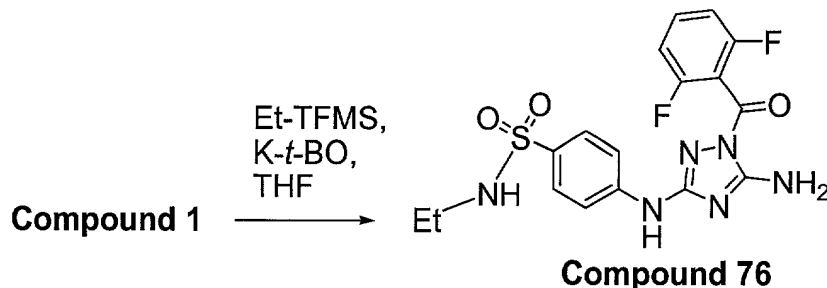
Example 10

4-[[5-amino-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-*N*-ethylbenzenesulfonamide (Cpd 76)

Compound 1 (100 mg, 0.254 mmol) was reacted with 1.2 equivalents of ethyl

10 trifluoromethanesulfonate (Et-TFMS) (40 μL, 0.305 mmol), and 1.5 equivalents of potassium *t*-butoxide (K-*t*-BO) (0.38 mmol, 381 μL of a 1.0 M THF solution) in THF

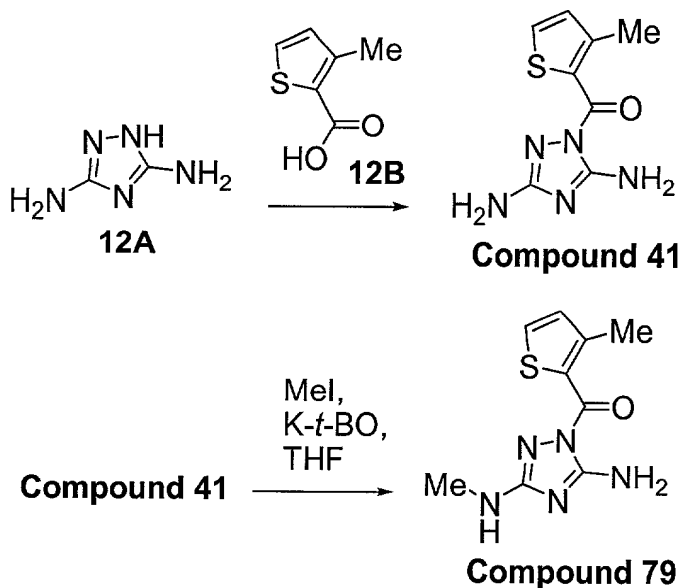
(5 mL) at 50 °C, stirring for 16 hours. Purification of the reaction mixture by column chromatography in 10% methanol/methylene chloride gave the product Compound **76** (27.1 mg, 25% yield). ¹H NMR (400MHz, (CD₃)₂SO) δ 9.87 (s, 1H), 8.00 (s, 2H), 7.76-7.68 (m, 1H), 7.55-7.48 (m, 4H), 7.34 (t, 2H), 7.22 (t, 1H), 2.73-2.67 (m, 2H), 0.94 (t, 3H); MS (ESI) m/z: 423 (M+H⁺)



Example 12

*N*³-methyl-1-[(3-methyl-2-thienyl)carbonyl]-1*H*-1,2,4-triazole-3,5-diamine (Cpd **79**)

Using the procedure of Example 1, 3,5-diamino-1,2,4-triazole Compound **12A** was acylated with 3-methylthiophene-2-carboxylic acid Compound **12B** mediated by DIC/HOBt in anhydrous DMF to produce Compound **41** (72% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 7.88 (d, J=4.5, 1H), 7.59 (s, 2H), 7.05 (d, J=4.8, 1H), 5.78 (s, 2H), 2.55 (s, 3H); MS (ESI) m/z: 224.1 (M+H⁺), 245.9 (M+Na⁺). Compound **41** (0.45 mmol, 100 mg) was reacted with 3 equivalents of iodomethane (1.34 mmol, 84 uL) and 1.1 equivalents of potassium t-butoxide (0.49 mmol, 493 uL of 1.0 M THF solution) in THF (5 mL), stirring 16 hours at 25 °C. Purification by column chromatography (eluting with 10% methanol/dichloromethane) gave the product Compound **79** (7.7 mg, 7% yield). ¹H NMR (400MHz, (CD₃)₂SO) δ 9.80 (s, 1H), 7.60 (d, 1H), 6.96 (d, 1H), 6.17 (s, 2H), 3.47 (s, 3H), 2.40 (s, 3H); MS (ESI) m/z: 238 (M+H⁺), 260 (M+Na⁺).

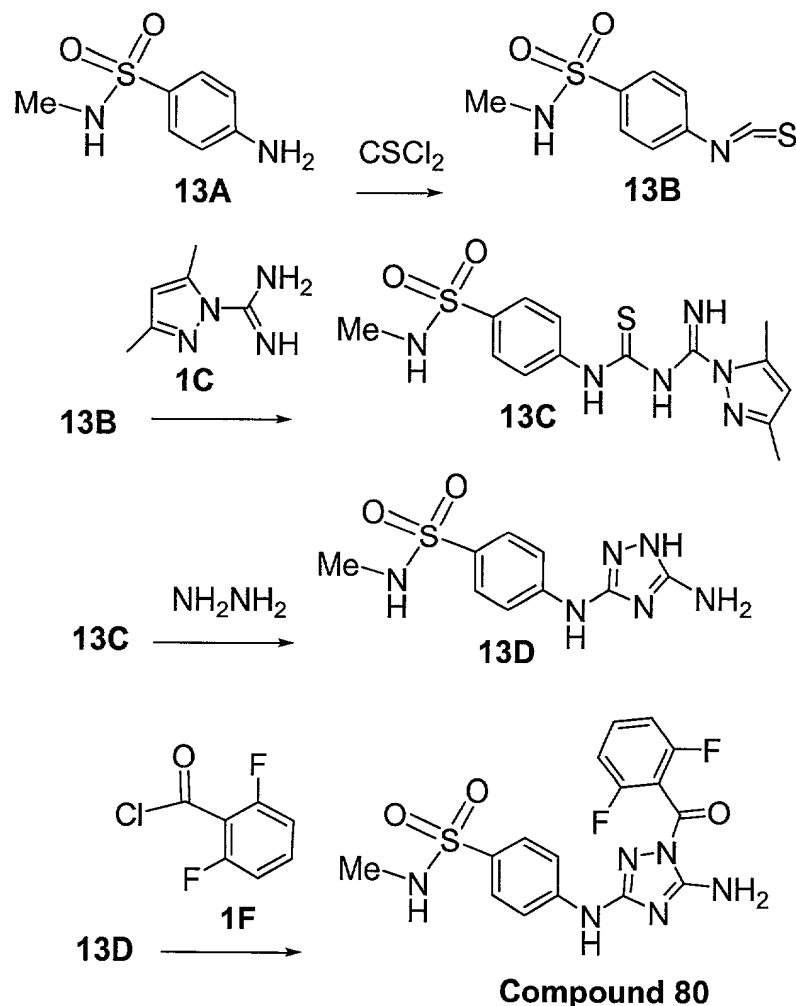


Example 13

4-[[5-amino-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-*N*-methylbenzenesulfonamide (Cpd 80)

t-BuOK (23.1 mL, 1.0 M solution in *t*-BuOH, 23.1 mmol) was added dropwise to a solution of 4-isothiocyanato-*N*-methylbenzenesulfonamide Compound 13B (prepared using the procedure of Example 1) (4.8 g, 21.0 mmol) and 2,5-dimethylpyrazole-1-carboximidine nitrate Compound 1C (4.2 g, 21.0 mmol) in DMF (20 mL). The mixture was heated to 60 °C for 2 h, then poured into ice. The precipitate was collected by filtration and washed with water, then air dried to afford 4-[3-(3,5-dimethylpyrazol-1-yliminomethyl)thioureido]-*N*-methylbenzenesulfonamide Compound 13C as a yellow solid (7.3 g, 95% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 8.01 (s, 1H), 7.71 (m, 4H), 6.15 (s, 1H), 2.40 (s, 3H), 2.22 (s, 6H); MS (ESI) *m/z*: 367 (M+H⁺). Hydrazine (3.3 g, 110.0 mmol) at 0 °C was added to a suspension of 4-[3-(3,5-dimethylpyrazol-1-yliminomethyl)thioureido]-*N*-methylbenzenesulfonamide Compound 13C (2.0 g, 5.5 mmol) in THF (20 mL). The mixture was heated to 60 °C for 2 hrs, then poured into ice. The precipitate was collected by filtration, washed with water and CH₂Cl₂, then air dried to produce Compound 13D as a white solid (1.3 g, 87% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 11.36 (s, 1H), 9.31 (s, 1H), 7.63 (q, 4H), 7.09 (q, 1H), 6.05 (s, 2H), 2.39 (d, 3H); MS (ESI) *m/z*: 269 (M+H⁺). Using the procedure of Example 1, Compound 13D was acylated with 2,6-difluorobenzoyl chloride Compound 1F in anhydrous pyridine to produce Compound 80 (80% yield). ¹H NMR (300 MHz,

CD₃OD) δ 7.64 (m, 1H), 7.63 (d, 2H), 7.53 (d, 2H), 7.15 (t, 2H), 2.43 (s, 3H); MS (ESI) m/z : 409 (M+H⁺).



5

Using the procedure for Example 13, the following compounds were prepared by acylation of the intermediate Compound **13D** using the indicated starting material in place of Compound **1F** and reagent(s):

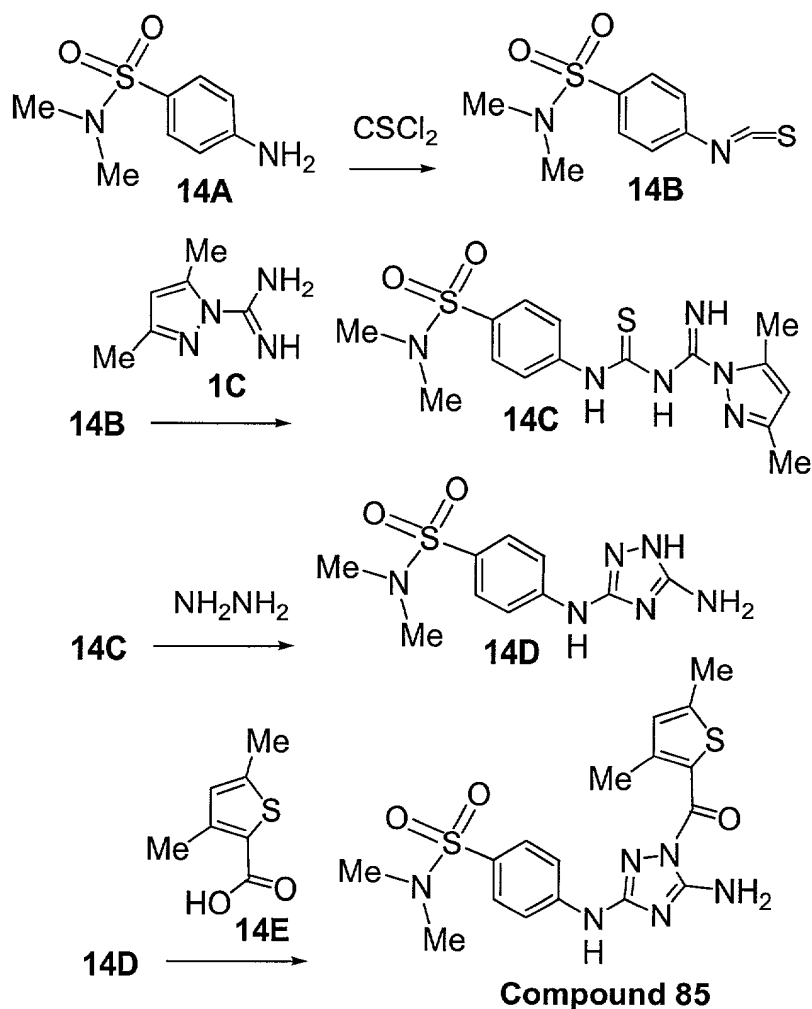
Cpd	Name/Data	Starting Mat'l
81	4-[[5-amino-1-(2,6-difluoro-3-methylbenzoyl)-1H-1,2,4-triazol-3-yl]amino]-N-methylbenzenesulfonamide	2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine
	¹ H NMR (300 MHz, CD ₃ OD) δ 7.55 (d, 2H), 7.48-7.44 (m, 1H), 7.46 (d, 2H), 2.42 (s, 3H), 2.25 (s, 3H); MS (ESI) m/z : 423 (M+H ⁺)	

82	4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -methylbenzenesulfonamide	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.92 (s, 1H), 8.03 (d, 1H), 7.81 (d, 2H), 7.69 (d, 2H), 7.14 (m, 2H), 2.62 (s, 3H), 2.55 (s, 3H); MS (ESI) m/z: 393 (M+H ⁺)	
83	4-[[5-amino-1-[(3,5-dimethyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -methylbenzenesulfonamide	3,5-dimethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.89 (s, 1H), 8.09 (d, 1H), 7.74 (d, 2H), 7.63 (d, 2H), 7.02 (d, 1H), 2.94 (q, 2H), 2.32 (s, 3H), 1.33 (t, 3H); MS (ESI) m/z: 407 (M+H ⁺)	
84	4-[[5-amino-1-[(5-ethyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -methylbenzenesulfonamide	5-ethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.65 (s, 1H), 7.64 (d, 1H), 7.50 (d, 2H), 7.69 (d, 2H), 6.66 (s, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 2.12 (s, 3H); MS (ESI) m/z: 407 (M+H ⁺)	

Example 14

1-[(3,5-dimethyl-2-thienyl)carbonyl]-*N*³-[4-(1*H*-imidazol-1-yl)phenyl]-1*H*-1,2,4-triazole-3,5-diamine (Cpd **85**)

- 5 4-Isothiocyanato-*N,N*-dimethylbenzenesulfonamide Compound **14B** (prepared using the procedure of Example 1) (1.8 g, 7.4 mmol) was reacted with 2,5-dimethylpyrazole-1-carboximidine nitrate Compound **1C** (1.5 g, 7.4 mmol) and *t*-BuOK (7.4 mL, 1.0 M solu in *t*-BuOH, 7.4 mmol) to produce 4-[3-(3,5-dimethylpyrazol-1-yliminomethyl)thioureido]-*N,N*-dimethylbenzenesulfonamide Compound **14C** as a
- 10 yellow solid (2.5 g, 89% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 10.05 (s, 1H), 8.91 (s, 1H), 7.67 (m, 4H), 6.15 (s, 1H), 2.57 (s, 6H), 2.18 (s, 6H); MS (ESI) m/z: 381 (M+H⁺). Compound **14C** (2.5 g, 6.6 mmol) was reacted with hydrazine (4.2 g, 132.0 mmol) to produce 1.7 g (90 %) of Compound **14D** as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.47 (s, 1H), 7.81 (d, 2H), 7.75 (d, 2H), 6.10 (s, 1H), 2.67 (s, 6H);
- 15 MS (ESI) m/z: 283 (M+H⁺). Compound **14D** was acylated with 3,5-dimethylthiophene-2-carboxylic acid Compound **1F** mediated by DIC/HOBt in DMF to produce Compound **85** (52% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.93 (s, 1H), 7.88 (d, 2H), 7.85 (s, 1H), 7.65 (d, 2H), 6.90 (s, 1H), 2.60 (s, 6H), 2.56 (s, 3H), 2.54 (s,

3H); MS (ESI) m/z : 421 ($M+H^+$).

Using the procedure for Example 14, the following compounds were prepared by

- 5 acylation of the intermediate Compound 14D using the indicated starting material in place of Compound 14E and reagent(s):

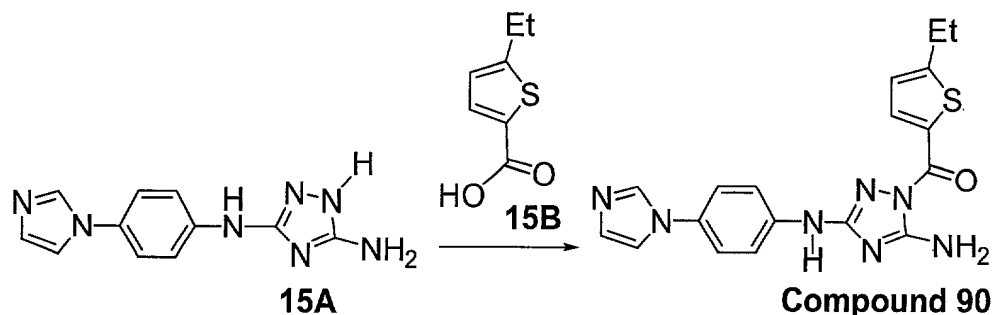
Cpd	Name/Data	Starting Mat'l
86	4-[[5-amino-1-[(5-ethyl-2-thienyl)carbonyl]-1H-1,2,4-triazol-3-yl]amino]-N,N-dimethyl-benzenesulfonamide 1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.03 (s, 1H), 8.13 (d, 1H), 7.91 (s, 1H), 7.86 (d, 2H), 7.66 (d, 2H), 7.10 (d, 2H), 2.95 (q, 2H), 2.56 (s, 6H), 1.32 (t, 3H); MS (ESI) m/z : 421 ($M+H^+$)	5-ethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
87	4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1H-1,2,4-triazol-3-yl]amino]-N,N-dimethyl-benzenesulfonamide 1H NMR (300 MHz, $(CD_3)_2SO$) δ 10.01 (s, 1H), 8.05 (d, 1H), 7.86 (d, 3H), 7.69 (d, 2H), 7.13 (d, 1H), 2.63 (s, 3H), 2.55 (s, 6H); MS (ESI) m/z : 407 ($M+H^+$)	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF

88	4-[[5-amino-1-(2,6-difluoro-3-methylbenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N,N</i> -dimethyl-benzenesulfonamide	2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine
	¹ H NMR (300 MHz, CDCl ₃) δ 7.79 (s, 1H), 7.55 (d, 2H), 7.40 (d, 2H), 7.35 (m, 1H), 6.95 (s, 2H), 6.92 (m, 1H), 2.65 (s, 6H), 2.27 (s, 3H); MS (ESI) <i>m/z</i> : 437 (M+H ⁺)	
89	4-[[5-amino-1-(2,6-difluorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N,N</i> -dimethyl-benzenesulfonamide	2,6-difluorobenzoyl chloride in anhydrous pyridine
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.74 (s, 1H), 7.77 (s, 2H), 7.50-7.40 (m, 1H), 7.30-7.20 (m, 4H), 7.10 (m, 2H), 2.25 (s, 6H); MS (ESI) <i>m/z</i> : 423 (M+H ⁺)	

Example 15

1-[(5-ethyl-2-thienyl)carbonyl]-*N*³-[4-(1*H*-imidazol-1-yl)phenyl]-1*H*-1,2,4-triazole-3,5-diamine (Cpd **90**)

- 5 Using the published procedure (Webb et al., *J. Heterocyclic Chem.*, **1987**, 24, 275-278), 4-imidazol-1-yl-aniline (0.50 g, 3.14 mmol), diphenyl cyanocarbonimidate (0.75 g, 3.14 mmol) and THF (30 mL) were combined in a nitrogen purged flask. The mixture was refluxed for 2 hrs, then cooled down to ice temperature and hydrazine (31.4 mL, 1.0 M solution in THF, 31.4 mmol) was added dropwise. The mixture was then
- 10 refluxed for 2 hrs. The precipitate was filtered and collected, washed with ethyl acetate and air dried to produce the intermediate Compound **15A** (0.60 g, 79 %). ¹H NMR (300 MHz, (CD₃)₂SO) δ 11.15 (s, 1H), 8.85 (s, 1H), 8.05 (s, 1H), 7.57 (s, 1H), 7.48 (d, 2H), 7.35 (d, 2H), 7.04 (s, 1H), 5.85 (s, 2H); MS (ESI) *m/z*: 242 (M+H⁺). Using the procedure of Example 1, Compound **15A** was acylated with 5-ethylthiophene-2-
- 15 carboxylic acid Compound **15B** mediated by DIC/HOBt in DMF to provide Compound **90** (59 % yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.63 (s, 1H), 8.14 (d, 1H), 7.85-7.70 (m, 7H), 7.56-7.53 (m, 2H), 7.07 (d, 2H), 2.95 (q, 2H), 1.33 (t, 3H); MS (ESI) *m/z*: 380 (M+H⁺).



Using the procedure for Example 15, the following compounds were prepared by acylation of the intermediate Compound **15A** using the indicated starting material in place of Compound **15B** and reagent(s):

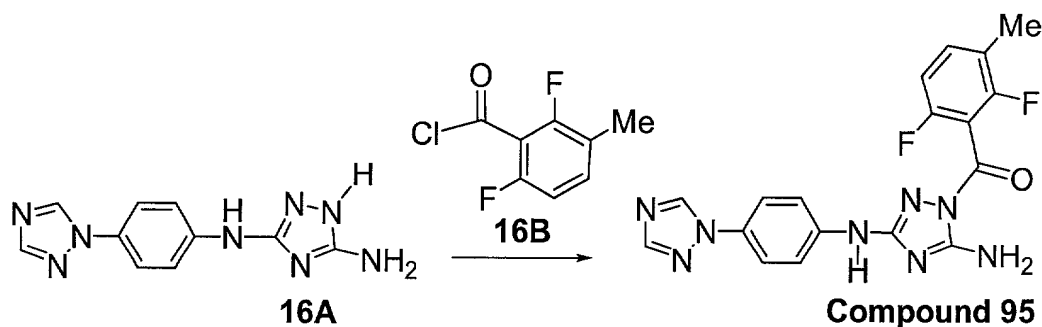
Cpd	Name/Data	Starting Mat'l
91	<i>N</i> ³ -[4-(1 <i>H</i> -imidazol-1-yl)phenyl]-1-[(3-methyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.62 (s, 1H), 7.97 (d, 1H), 7.92 (s, 1H), 7.82-7.72 (m, 5H), 7.56-7.53 (m, 2H), 7.11 (d, 1H), 2.61 (s, 3H); MS (ESI) <i>m/z</i> : 366 (M+H ⁺)	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
92	1-[(3,5-dimethyl-2-thienyl)carbonyl]- <i>N</i> ³ -[4-(1 <i>H</i> -imidazol-1-yl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.51 (s, 1H), 8.15 (s, 1H), 7.75 (m, 4H), 7.61 (s, 1H), 7.53 (d, 2H), 7.05 (s, 1H), 6.85 (s, 1H), 2.53 (s, 3H), 2.52 (s, 3H); MS (ESI) <i>m/z</i> : 380 (M+H ⁺)	3,5-dimethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
93	1-(2,6-difluorobenzoyl)- <i>N</i> ³ -[4-(1 <i>H</i> -imidazol-1-yl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.52 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.70 (p, 1H), 7.57 (s, 1H), 7.45 (d, 2H), 7.36 (d, 2H), 7.30 (t, 2H), 7.01 (s, 1H); MS (ESI) <i>m/z</i> : 382 (M+H ⁺)	2,6-difluorobenzoyl chloride in anhydrous pyridine
94	1-(2,6-difluoro-3-methylbenzoyl)- <i>N</i> ³ -[4-(1 <i>H</i> -imidazol-1-yl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.52 (s, 1H), 8.08 (s, 1H), 7.93 (s, 1H), 7.57 (s, 1H), 7.53 (m, 1H), 7.42 (d, 2H), 7.35 (d, 2H), 7.18 (t, 1H), 7.02 (s, 1H), 2.25 (s, 3H); MS (ESI) <i>m/z</i> : 396 (M+H ⁺)	2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine

Example 16

1-(2,6-difluoro-3-methylbenzoyl)-*N*³-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-1*H*-1,2,4-triazole-3,5-diamine (Cpd **95**)

Using the procedure of Example 15, 4-(1,2,4-triazol-1-yl)-aniline (0.35 g, 2.18 mmol), diphenyl cyanocarbonimidate (0.52 g, 2.18 mmol) and hydrazine (21.8 mL, 1.0 M solution in THF, 21.8 mmol) were reacted to produce Compound **16D** (0.40 g, 78% yield) as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 11.21 (s, 1H), 9.06 (s, 1H), 8.92 (s, 1H), 8.13 (s, 1H), 7.61 (m 4H), 5.87 (s, 2H); MS (ESI) m/z: 243 (M+H⁺).

Using the procedure of Example 1, Compound **16D** was acylated with 2,6-difluoro-3-methylbenzoyl chloride Compound **16B** in anhydrous pyridine to produce Compound **95** (51% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.62 (s, 1H), 9.11 (s, 1H), 8.12 (s, 1H), 7.91 (s, 1H), 7.56 (d, 2H), 7.60-7.50 (q, 1H), 7.45 (d, 2H), 7.16 (t, 1H), 2.25 (s, 3H); MS (ESI) m/z: 397 (M+H⁺).



Using the procedure for Example 16, the following compounds were prepared by acylation of the intermediate Compound **16A** using the indicated starting material in place of Compound **16B** and reagent(s):

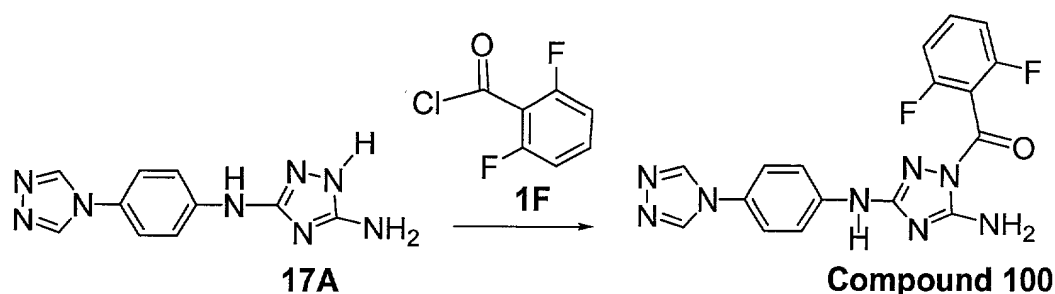
Cpd	Name/Data	Starting Mat'l
96	1-(2,6-difluorobenzoyl)-N ³ -[4-(1H-1,2,4-triazol-1-yl)phenyl]-1H-1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.61 (s, 1H), 9.05 (s, 1H), 8.07 (s, 1H), 7.85 (s, 2H), 7.63 (p, 1H), 7.53 (d, 2H), 7.41 (d, 2H), 7.30 (t, 2H), 7.29 (t, 2H); MS (ESI) m/z: 383 (M+H ⁺)	2,6-difluorobenzoyl chloride in anhydrous pyridine
97	1-[(5-ethyl-2-thienyl)carbonyl]-N ³ -[4-(1H-1,2,4-triazol-1-yl)phenyl]-1H-1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.72 (s, 1H), 9.15 (s, 1H), 8.17 (s, 1H), 8.16 (d, 1H), 7.78 (s, 2H), 7.77 (d, 2H), 7.72 (d, 2H), 7.04 (d, 1H), 2.96 (q, 2H), 1.33 (t, 3H); MS (ESI) m/z: 381 (M+H ⁺)	5-ethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF

98	1-[(3,5-dimethyl-2-thienyl)carbonyl]- <i>N</i> ³ -[4-(1 <i>H</i> -1,2,4-triazol-1-yl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine	3,5-dimethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.67 (s, 1H), 9.15 (s, 1H), 8.18 (s, 1H), 7.75 (m, 6H), 6.89 (s, 1H), 2.52 (s, 3H), 2.51 (s, 3H); MS (ESI) <i>m/z</i> : 381 (M+H ⁺)	
99	1-[(3-methyl-2-thienyl)carbonyl]- <i>N</i> ³ -[4-(1 <i>H</i> -1,2,4-triazol-1-yl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.68 (s, 1H), 9.13 (s, 1H), 8.16 (s, 1H), 7.99 (d, 1H), 7.77 (m, 6H), 7.12 (d, 1H); MS (ESI) <i>m/z</i> : 367 (M+H ⁺)	

Example 17

1-(2,6-difluorobenzoyl)-*N*³-[4-(4*H*-1,2,4-triazol-4-yl)phenyl]-1*H*-1,2,4-triazole-3,5-diamine (Cpd 100)

- 5 Using the procedure of Example 15, 4-(1,3,4-triazol-1-yl)-aniline (1.35 g, 8.43 mmol), diphenyl cyanocarbonimidate (2.00 g, 8.43 mmol) and hydrazine (84.3 mL, 1.0 M solution in THF, 84.3 mmol) were reacted to provide Compound **17A** (1.10 g, 77% yield) as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 8.90 (s, 2H), 7.62 (d, 2H), 7.36 (d, 2H), 5.82 (s, 2H); MS (ESI) *m/z*: 243 (M+H⁺). Using the procedure of
- 10 Example 1, Compound **17A** was acylated with 2,6-difluorobenzoyl chloride Compound **1F** in anhydrous pyridine to provide Compound **100** (36% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.61 (s, 1H), 8.98 (s, 2H), 7.96 (s, 2H), 7.67 (p, 1H), 7.47 (d, 2H), 7.42 (d, 2H), 7.32 (t, 2H); MS (ESI) *m/z*: 383 (M+H⁺).



15

Using the procedure for Example 17, the following compounds were prepared by acylation of the intermediate Compound **17D** using the indicated starting material in place of Compound **1F** and reagent(s):

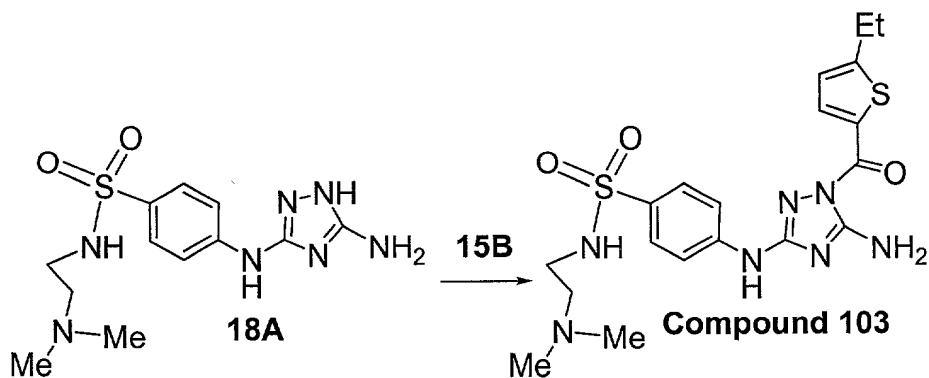
Cpd	Name/Data	Starting Mat'l
-----	-----------	----------------

101	1-(2,6-difluoro-3-methylbenzoyl)- <i>N</i> ³ -[4-(4 <i>H</i> -1,2,4-triazol-4-yl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine	2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.61 (s, 1H), 8.94 (s, 2H), 7.91 (s, 2H), 7.55 (q, 1H), 7.43 (q, 4H), 7.18 (t, 1H); MS (ESI) <i>m/z</i> : 397 (M+H ⁺)	
102	1-[(3-methyl-2-thienyl)carbonyl]- <i>N</i> ³ -[4-(4 <i>H</i> -1,2,4-triazol-4-yl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
	¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 10.22 (s, 1H), 9.04 (s, 2H), 7.95 (m, 3H), 7.67 (d, 2H), 7.07 (d, 1H), 6.13 (s, 2H); MS (ESI) <i>m/z</i> : 367 (M+H ⁺)	

Example 18

4-[[5-amino-1-[(5-ethyl-2-thienyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]-*N*-[2-(dimethylamino)ethyl]-benzenesulfonamide (Cpd **103**)

- 5 Using the procedure of Example 15, 4-amino-*N*-(2-dimethylaminoethyl)-benzenesulfonamide (2.00 g, 8.22 mmol), diphenyl cyanocarbonimide (2.00 g, 8.22 mmol) and hydrazine (82.3 mL, 1.0 M solution in THF, 82.3 mmol) were reacted to produce Compound **18A** (1.35 g, 50% yield) as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.22 (s, 1H), 8.43 (s, 1H), 7.55 (m, 4H), 7.02 (s, 1H), 5.91 (s, 2H), 2.71 (t, 2H), 2.15 (t, 2H), 2.05 (s, 6H); MS (ESI) *m/z*: 326 (M+H⁺). Using the procedure of
- 10 Example 1, Compound **18A** was acylated with 5-ethylthiophene-2-carboxylic acid Compound **15B** mediated by DIC/HOBt in DMF to produce Compound **103** (40% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 10.02 (s, 1H), 8.13 (d, 1H), 7.88 (s, 1H), 7.75 (d, 2H), 7.71 (d, 2H), 7.07 (d, 1H), 7.01 (s, 2H), 2.95 (q, 2H), 2.75 (t, 2H), 2.20 (t, 2H),
- 15 2.04 (s, 6H), 1.35 (t, 3H); MS (ESI) *m/z*: 464 (M+H⁺).



Using the procedure for Example 18, the following compounds were prepared by acylation of the intermediate Compound **18A** using the indicated starting material in

place of Compound **15B** and reagent(s):

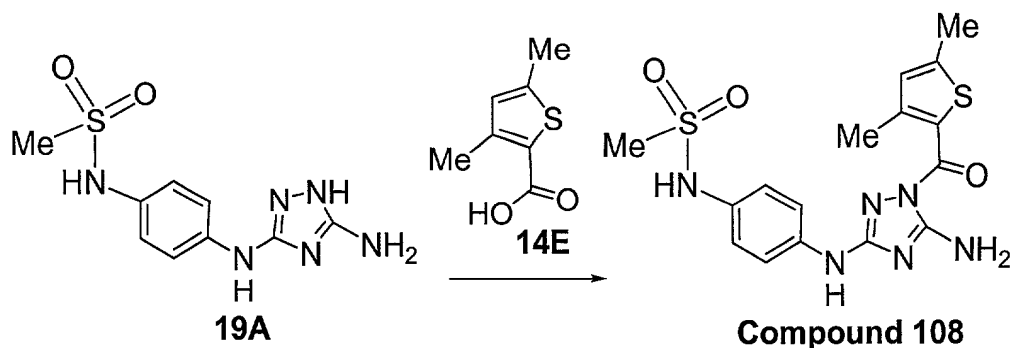
Cpd	Name/Data	Starting Mat'l
104	4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -[2-(dimethylamino)ethyl]-benzenesulfonamide ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.89 (s, 1H), 8.04 (d, 1H), 7.83 (s, 1H), 7.79 (d, 2H), 7.71 (d, 2H), 7.15 (s, 2H), 7.08 (d, 1H), 2.76 (t, 2H), 2.61 (s, 3H), 2.21 (t, 2H), 2.07 (s, 6H); MS (ESI) <i>m/z</i> : 450 (M+H ⁺)	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
105	4-[[5-amino-1-(2,6-difluoro-3-methylbenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -[2-(dimethylamino)ethyl]-benzenesulfonamide ¹ H NMR (300 MHz, CD ₃ OD) δ 7.57 (d, 2H), 7.45 (m, 3H), 7.00 (t, 1H), 2.86 (t, 2H), 2.32 (t, 2H), 2.25 (s, 3H), 2.11 (s, 6H); MS (ESI) <i>m/z</i> : 480 (M+H ⁺)	2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine
106	4-[[5-amino-1-(2,6-difluorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -[2-(dimethylamino)ethyl]-benzenesulfonamide ¹ H NMR (300 MHz, CD ₃ OD) δ 7.60 (m, 1H), 7.55 (d, 2H), 7.45 (d, 2H), 7.11 (t, 1H), 2.87 (t, 2H), 2.32 (t, 2H), 2.12 (s, 6H); MS (ESI) <i>m/z</i> : 466 (M+H ⁺)	2,6-difluorobenzoyl chloride in anhydrous pyridine
107	4-[[5-amino-1-[(3,5-dimethyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -[2-(dimethylamino)ethyl]-benzenesulfonamide ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.89 (s, 1H), 7.81 (m, 4H), 7.71 (d, 2H), 7.22 (s, 1H), 6.86 (s, 1H), 2.79 (t, 2H), 2.63 (s, 3H), 2.61 (s, 3H), 2.21 (t, 6H), 2.06 (s, 6H); MS (ESI) <i>m/z</i> : 464 (M+H ⁺)	3,5-dimethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF

Example 19

N-[4-[[5-amino-1-[(3,5-dimethyl-2-thienyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]phenyl]-methanesulfonamide (Cpd **108**)

Using the procedure of Example 15, *N*-(4-aminophenyl)methanesulfonamide (2.00 g, 10.70 mmol), diphenyl cyanocarbonimide (2.60 g, 10.70 mmol), and hydrazine (107.0 mL, 1.0 M solution in THF, 107.0 mmol) were reacted to produce Compound **19A** (1.30 g, 45% yield) as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 8.80 (s, 1H), 8.55 (s, 1H), 7.43 (d, 2H), 6.96 (d, 2H), 5.75 (s, 2H), 2.82 (s, 3H); MS (ESI) *m/z*: 269 (M+H⁺). Using the procedure of Example 1, Compound **19A** was acylated with 3,5-dimethylthiophene-2-carboxylic acid Compound **19B** mediated by DIC/HOBt in DMF

to provide Compound **108** (11% yield). ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.30 (s, 1H), 9.25 (s, 1H), 7.70 (s, 1H), 7.61 (d, 2H), 7.12 (d, 2H), 6.83 (s, 1H), 2.87 (s, 3H), 2.50 (s, 3H); MS (ESI) m/z : 407 ($\text{M}+\text{H}^+$).



Using the procedure for Example 19, the following compounds were prepared by acylation of the intermediate Compound **19A** using the indicated starting material in place of Compound **14E** and reagent(s):

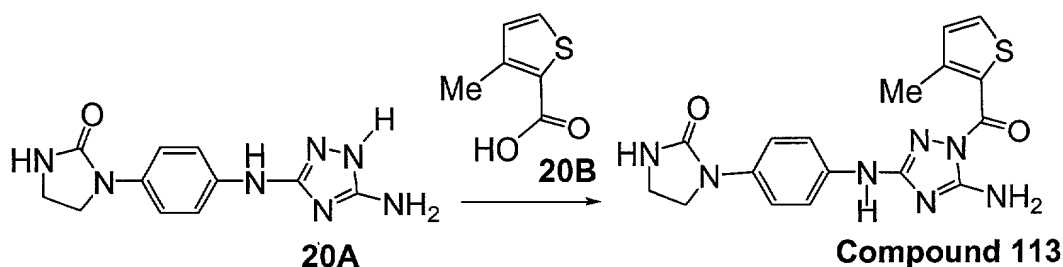
Cpd	Name/Data	Starting Mat'l
109	<i>N</i> -[4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]phenyl]-methanesulfonamide ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.35 (s, 1H), 9.30 (s, 1H), 8.01 (d, 1H), 7.75 (s, 1H), 7.62 (d, 2H), 7.12 (m, 3H), 6.83 (s, 1H), 2.89 (s, 3H), 2.59 (s, 3H); MS (ESI) m/z : 393 ($\text{M}+\text{H}^+$)	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
110	<i>N</i> -[4-[[5-amino-1-[(5-ethyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]phenyl]-methanesulfonamide ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.37 (s, 1H), 9.30 (s, 1H), 8.12 (d, 1H), 7.74 (s, 1H), 7.62 (d, 2H), 7.12 (d, 2H), 7.03 (d, 1H), 2.95 (q, 2H), 2.89 (s, 3H), 1.35 (t, 3H); MS (ESI) m/z : 407 ($\text{M}+\text{H}^+$)	5-ethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
111	<i>N</i> -[4-[[5-amino-1-(2,6-difluorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]phenyl]-methanesulfonamide ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ 9.32 (s, 1H), 9.21 (s, 1H), 7.88 (s, 2H), 7.64 (p, 1H), 7.25 (m, 4H), 6.92 (d, 2H), 2.82 (s, 3H); MS (ESI) m/z : 409 ($\text{M}+\text{H}^+$)	2,6-difluorobenzoyl chloride in anhydrous pyridine

- 112** *N*-[4-[[5-amino-1-(2,6-difluoro-3-methylbenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]phenyl]-methanesulfonamide
¹H NMR (300 MHz, (CD₃)₂SO) δ 9.33 (s, 1H), 7.88 (s, 2H), 7.54 (q, 1H), 7.25 (d, 2H), 7.16 (t, 1H), 6.92 (d, 2H), 2.82 (s, 3H), 2.25 (s, 3H); MS (ESI) *m/z*: 423 (M+H⁺)
- 2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine

Example 20

1-[4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1*H*-1,2,4-triazol-3-yl]amino]phenyl]-2-imidazolidinone (Cpd **113**)

- 5 Using the procedure of Example 15, 1-(4-aminophenyl)imidazolidin-2-one (0.24 g, 1.35 mmol), diphenyl cyanocarbonimidate (0.32 g, 1.35 mmol) and hydrazine (13.5 mL, 1.0 M solution in THF, 13.5 mmol) were reacted to produce Compound **20A** (0.28 g, 80%) as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 11.05 (s, 1H), 8.42 (s, 1H), 7.35 (d, 2H), 7.24 (d, 2H), 6.65 (s, 1H), 5.78 (s, 2H), 3.74 (t, 2H), 3.32 (t, 2H); MS
- 10 (ESI) *m/z*: 260 (M+H⁺). Using the procedure of Example 1, Compound **20A** was acylated with 3-methylthiophene-2-carboxylic acid Compound **20B** mediated by DIC/HOBt in DMF to provide Compound **113** (41% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.21 (s, 1H), 8.01 (d, 1H), 7.68 (s, 1H), 7.55 (d, 2H), 7.43 (d, 2H), 7.11 (d, 1H), 6.71 (s, 1H), 3.83 (q, 2H), 3.37 (q, 2H), 2.63 (s, 3H); MS (ESI) *m/z*: 384 (M+H⁺).



- Using the procedure for Example 20, the following compounds were prepared by acylation of the intermediate Compound **20A** using the indicated starting material in place of Compound **20B** and reagent(s):

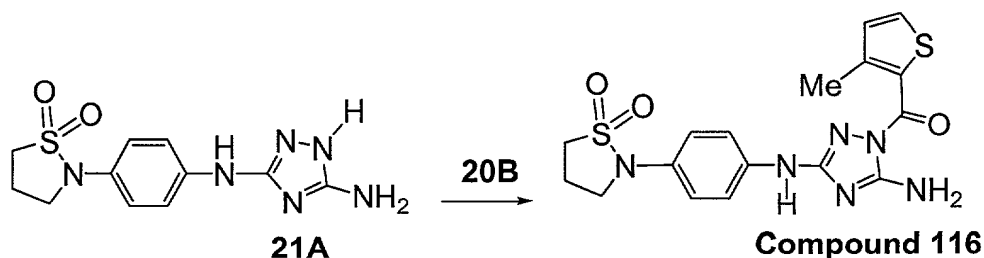
Cpd	Name/Data	Starting Mat'l
114	1-[4-[[5-amino-1-(2,6-difluoro-3-methylbenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]phenyl]-2-imidazolidinone ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.12 (s, 1H), 7.82 (s, 2H), 7.50 (m, 1H), 7.21 (m, 4H), 7.20 (m, 1H), 6.70 (s, 1H), 3.72 (t, 2H), 3.28 (t, 3H), 2.21 (s, 3H); MS (ESI) m/z: 414 (M+H ⁺)	2,6-difluoro-3-methylbenzoyl chloride in anhydrous pyridine
115	1-[4-[[5-amino-1-(2,6-difluorobenzoyl)-1 <i>H</i> -1,2,4-triazol-3-yl]amino]phenyl]-2-imidazolidinone ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.16 (s, 1H), 7.87 (s, 2H), 7.63 (m, 1H), 7.19 (m, 6H), 6.74 (s, 1H), 3.72 (t, 2H), 3.28 (t, 3H); MS (ESI) m/z: 400 (M+H ⁺)	2,6-difluorobenzoyl chloride in anhydrous pyridine

Example 21

*N*³-[4-(1,1-dioxido-2-isothiazolidinyl)phenyl]-1-[(3-methyl-2-thienyl)carbonyl]-1*H*-1,2,4-triazole-3,5-diamine (Cpd 116)

- 5 Using the procedure of Example 15, 4-(1,1-dioxoisothiazolidin-2-yl)phenylamine (0.92 g, 4.36 mmol), diphenyl cyanocarbonimidate (1.10 g, 4.36 mmol) and hydrazine (43.6 mL, 1.0 M solution in THF, 43.6 mmol) were reacted to produce Compound **21A** (1.2 g, 95%) as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 11.05 (s, 1H), 8.58 (s, 1H), 7.47 (d, 2H), 7.05 (d, 2H), 5.78 (s, 1H), 3.55 (t, 2H), 3.32 (t, 2H), 2.30 (p, 2H); MS
- 10 (ESI) m/z: 295 (M+H⁺). Using the procedure of Example 1, Compound **21A** was acylated with 3-methylthiophene-2-carboxylic acid Compound **20B** mediated by DIC/HOBt in DMF to produce Compound **116** (48% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.38 (s, 1H), 8.01 (d, 1H), 7.73 (s, 2H), 7.62 (d, 2H), 7.15 (d, 2H), 7.08 (d, 1H), 3.67 (t, 2H), 3.42 (t, 2H), 2.58 (s, 3H), 2.35 (p, 2H); MS (ESI) m/z: 419 (M+H⁺).

15



Using the procedure for Example 21, the following compounds were prepared by acylation of the intermediate Compound **21A** using the indicated starting material in

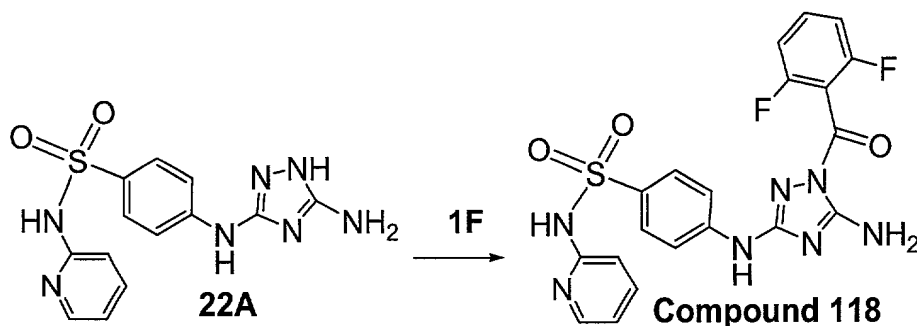
place of Compound **20B** and reagent(s):

Cpd	Name/Data	Starting Mat'l
117	1-(2,6-difluorobenzoyl)- <i>N</i> ³ -[4-(1,1-dioxido-2-isothiazolidinyl)phenyl]-1 <i>H</i> -1,2,4-triazole-3,5-diamine ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.31 (s, 1H), 7.80 (s, 2H), 7.62 (t, 2H), 7.28 (m, 3H), 7.01 (d, 2H), 3.63 (t, 2H), 3.35 (t, 2H), 2.32 (p, 2H); MS (ESI) <i>m/z</i> : 435 (M+H ⁺)	2,6-difluorobenzoyl chloride in anhydrous pyridine

Example 22

4-[[5-amino-1-(2,6-difluorobenzoyl)-1*H*-1,2,4-triazol-3-yl]amino]-*N*-(2-pyridinyl)-benzenesulfonamide (Cpd **118**)

Using the procedure of Example 15, 4-amino-*N*-pyridin-2-yl-benzenesulfonamide (1.48 g, 5.96 mmol), diphenyl cyanocarbonimidate (1.42 g, 5.96 mmol), and hydrazine (59.6 mL, 1.0 M solution in THF, 59.6 mmol) were reacted to provide Compound **22A** (0.98 g, 50%) as a white solid. ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.22 (s, 1H), 8.05 (s, 1H), 7.73 (m, 3H), 7.53 (d, 2H), 7.04 (d, 1H), 6.85 (m, 2H), 5.85 (s, 2H); MS (ESI) *m/z*: 332 (M+H⁺). Using the procedure of Example 1, Compound **22A** was acylated with 2,6-difluorobenzoyl chloride Compound **1F** in anhydrous pyridine to provide Compound **118** (61% yield). ¹H NMR (300 MHz, (CD₃)₂SO) δ 9.85 (s, 1H), 8.00-7.90 (m, 2H), 7.65 (m, 1H), 7.59 (d, 2H), 7.35 (d, 2H), 7.25 (t, 2H), 7.04 (d, 1H), 6.81 (t, 1H), 3.31 (s, 2H); MS (ESI) *m/z*: 472 (M+H⁺).



Using the procedure for Example 22, the following compounds were prepared by acylation of the intermediate Compound **22A** using the indicated starting material in place of Compound **1F** and reagent(s):

Cpd	Name/Data	Starting Mat'l
119	4-[[5-amino-1-[(5-ethyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -(2-pyridinyl)-benzenesulfonamide ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.87 (s, 1H), 8.11 (d, 1H), 8.01 (s, 1H), 7.90 (s, 1H), 7.75 (m, 4H), 7.68 (d, 2H), 7.63 (t, 1H), 7.07 (m, 2H), 6.85 (m, 1H), 2.95 (q, 2H), 1.32 (t, 3H); MS (ESI) m/z: 470 (M+H ⁺)	5-ethylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
120	4-[[5-amino-1-[(3,5-dimethyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -(2-pyridinyl)-benzenesulfonamide ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.84 (s, 1H), 7.98 (s, 1H), 7.91 (s, 1H), 7.74 (m, 4H), 7.71 (d, 2H), 7.63 (t, 1H), 7.07 (m 1H), 6.85 (m, 2H), 2.53 (s, 3H), 2.52 (s, 3H); MS (ESI) m/z: 470 (M+H ⁺)	3,5-dithylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF
121	4-[[5-amino-1-[(3-methyl-2-thienyl)carbonyl]-1 <i>H</i> -1,2,4-triazol-3-yl]amino]- <i>N</i> -(2-pyridinyl)-benzenesulfonamide ¹ H NMR (300 MHz, (CD ₃) ₂ SO) δ 9.85 (s, 1H), 8.02 (m, 2H), 7.79 (m, 4H), 7.73 (d, 2H), 7.63 (t, 1H), 7.13 (d, 1H), 7.07 (m 1H), 6.81 (m, 1H), 2.61 (s, 3H); MS (ESI) m/z: 456 (M+H ⁺)	3-methylthiophene-2-carboxylic acid mediated by DIC/HOBt in DMF

Biological Examples

The utility of the compounds to treat or ameliorate a cyclin dependent kinase and tyrosine kinase mediated disorders was determined using the following procedures.

5

Example 1

CDK1 Screening Assay

A kinase reaction mixture was prepared containing 50 mM Tris-HCl pH=8, 10 mM MgCl₂, 0.1 mM Na₃PO₄, 1 mM DTT, 10 μM ATP, 0.025 μM biotinylated histone-H1 peptide substrate and 0.2 μCuries per well ³³P-γ-ATP [2000-3000 Ci/mmol]. 70 μL of the kinase reaction mixture was dispensed into the well of a streptavidin coated FlashPlate™ (Cat. # SMP103, NEN, Boston, MA). Then 1 μL of test compound stock in 100% DMSO was added to the wells resulting in a final concentration of 1% DMSO in the reaction with a 100 μl final reaction volume. Next, CDK1:Cyclin-B protein was diluted in 50 mM Tris-HCl pH=8.0, 0.1% BSA at a concentration of 1 ng per μL and 30 μl (30ng enzyme per test well) was added to each well to initiate the reaction. The reaction was incubated for one hour at 30°C. At the end of the 1-hour incubation, the

15

reaction was terminated by aspirating the reaction mixture from the plate and washing the wells twice with PBS containing 100 mM EDTA. The histone-H1 biotinylated peptide substrate became immobilized on the Flashplate™ and the incorporation of ³³P-γ-ATP was measured by reading the plate on a scintillation counter. Inhibition of the enzymatic activity of CDK1 was measured by observing a reduced amount of ³³P-γ-ATP incorporated into the immobilized peptide.

VEGF-R Screening Assay

A kinase reaction mixture was prepared containing 50 mM Tris-HCl pH=8, 10 mM MgCl₂, 0.1 mM Na₃PO₄, 1 mM DTT, 10 μM ATP, 0.025 μM biotinylated peptide substrate and 0.8 μCuries per well ³³P-γ-ATP [2000-3000 Ci/mmol]. 70 μL of the kinase reaction mixture was dispensed into the well of a streptavidin coated FlashPlate™ (Cat. # SMP103, NEN, Boston, MA). Then 1 μL of test compound stock in 100% DMSO was added to the wells resulting in a final concentration of 1% DMSO in the reaction with a 100 μL final reaction volume. Next, soluble rat tyrosine kinase containing an N-terminal 6XHIS tag was diluted in 50 mM Tris-HCl pH=8.0, 0.1% BSA at a concentration of 5 ng per μL and 30 μL (150 ng enzyme per test well) was added to each well to initiate the reaction. The reaction was incubated for one hour at 30°C. At the end of the 1-hour incubation, the reaction was terminated by aspirating the reaction mixture from the plate and washing the wells twice with PBS containing 100 mM EDTA. The PLC1 biotinylated peptide substrate became immobilized on the Flashplate™ and the incorporation of ³³P-γ-ATP was measured by reading the plate on a scintillation counter. Inhibition of the enzymatic activity of the VEGF-R was measured by observing a reduced amount of ³³P-γ-ATP incorporated into the immobilized peptide.

IC₅₀ data for VEGF-R and CDK are shown in Table 1. IC₅₀ values listed as >10 or >100 indicate no observed 50% inhibition at the highest dose tested, nor was an inhibition maxima observed. ND means not tested.

Table 1

IC₅₀ (uM)

Cpd	CDK1	VEGF-R	HER2	CDK2
1	0.0064	0.1062	ND	ND
2	0.0032	0.3659	ND	ND
3	0.0080	0.3324	ND	ND
4	0.02232	0.3866	ND	ND
5	0.1436	0.5209	ND	ND
6	0.0394	8.144	ND	ND
7	0.057	>10	ND	ND
8	0.136	>100	ND	ND
9	0.039	1.597	ND	ND
10	0.252	0.4907	ND	ND
11	0.3046	>100	ND	ND
12	0.0454	0.08406	ND	ND
13	0.5353	0.5318	ND	ND
14	0.0045	0.0267	ND	ND
15	0.0048	0.0511	ND	ND
16	0.0021	0.0137	ND	ND
17	0.0025	0.027	ND	ND
18	0.067	0.058	ND	ND
19	0.0339	0.2907	ND	ND
20	0.0044	0.031	ND	ND
21	0.0088	0.023	ND	ND
22	0.0318	0.2334	ND	ND
23	0.0889	0.0353	ND	ND
24	0.2823	0.0674	ND	ND
25	0.01953	0.064	ND	ND
26	18.4	~100	ND	ND
27	~100	>100	ND	ND
28	0.9816	13.25	ND	ND
29	70.39	~100	ND	ND
30	0.017	0.0406	ND	ND
31	0.030	0.044	ND	ND
32	0.0031	0.0219	ND	ND
33	0.0032	0.0234	ND	ND

34	0.0016	0.0681	ND	ND
35	0.0011	0.0463	ND	ND
36	1.561	18.61	ND	ND
37	10.5	54.98	ND	ND
38	0.0299	0.8795	ND	ND
39	0.0122	0.3336	ND	ND
40	0.1949	11.06	ND	ND
42	0.1342	0.4433	ND	ND
43	0.0873	0.6279	ND	ND
44	0.5223	2.677	ND	ND
45	0.0137	0.3553	ND	ND
46	0.0358	0.4527	ND	ND
47	0.0586	2.523	ND	ND
48	2.603	~100	ND	ND
49	>1	>1	>1	ND
50	0.12	0.19	0.20	ND
51	0.007	0.019	0.031	ND
52	0.035	0.11	1.47	ND
53	>1	>1	>1	ND
54	0.55	14.0	6.1	ND
55	0.022	0.58	2.19	ND
56	0.49	20.0	4.17	ND
57	0.067	0.19	1.32	ND
58	0.014	0.42	0.65	ND
59	1.54	0.92	7.83	ND
60	1.37	0.89	7.46	ND
66	0.0006	0.032	0.060	0.0005
67	0.0037	0.038	0.052	0.0014
68	0.66	5.14	ND	ND
69	0.023	0.69	0.14	ND
70	0.035	0.91	1.23	ND
71	3.71	0.43	1.30	ND
72	1.43	0.38	1.49	ND
73	2.20	0.029	0.176	ND

74	0.46	0.021	0.062	ND
75	0.52	0.033	0.060	ND
76	0.012	0.53	~1	0.0044
78	0.0066	0.42	0.78	0.0017
79	>100	>100	>100	>100
80	0.0452	0.9346	1.1200	ND
81	0.0178	0.4822	1.6990	0.001
82	0.0090	0.0217	0.1183	ND
83	0.0084	0.0404	0.0130	ND
84	0.0038	0.0432	0.0516	ND
85	0.4126	0.1943	>1	ND
86	0.1087	0.0869	0.4128	ND
87	0.2171	0.0168	0.4357	ND
88	0.3134	0.9647	~1	ND
89	0.7096	0.5979	~10	ND
90	~1	~0.1	~0.1	ND
91	0.3349	0.0736	0.2233	ND
92	0.3493	0.1336	0.0558	ND
93	0.4525	0.7267	~1	ND
94	0.2716	0.4089	0.1469	ND
95	0.1387	0.2598	0.9138	ND
96	0.3726	0.8171	1.4080	ND
97	~0.1	~0.1	~0.01	ND
98	>0.1	~0.1	~0.1	ND
99	0.3656	0.098	0.0945	ND
100	0.3404	1.1000	1.2870	ND
101	0.1426	0.6498	0.8195	ND
102	2.3530	1.1010	2.2600	ND
103	0.0074	0.0449	0.2284	0.001
104	0.0156	0.0156	0.2033	0.001
105	0.0461	0.2756	0.8448	0.002
106	0.1250	0.5591	37.230	0.001
107	0.0138	0.0324	0.0297	0.002
108	0.0657	0.0307	0.0417	0.0120

109	0.1465	0.0252	0.1705	0.0210
110	0.0219	0.0136	0.0055	0.0050
111	0.1499	0.7019	16.830	ND
112	0.0870	0.7039	16.350	ND
113	0.2545	0.0302	0.0680	ND
114	0.2275	0.3125	1.3870	ND
115	0.3134	0.4666	1.4420	ND
116	0.0208	0.0261	0.1313	0.0010
117	0.0352	0.9080	5.4350	0.0070
118	0.33	0.397	>10	0.021
119	0.0672	0.0571	~1	0.0030
120	0.277	0.082	1.0	0.0090
121	0.0997	0.0272	0.7169	0.0030
122	2.21	>10	ND	ND
123	2.05	5.53	~100	0.031
128	0.0032	0.118	0.111	0.0033

Example 2

Kinase Selectivity Assays

Assays to test compound inhibition of other kinases were preformed using methods that measure the amount of phosphorylation of a biotinylated peptide substrate.

Biotinylated peptide substrates were selected from the literature as appropriate for the enzyme being evaluated. The general procedure used to assay for kinase activity is as follows: A kinase reaction mix was prepared in 50 mM Tris-HCl pH=8, 10 mM MgCl₂, 0.1 mM Na₃VO₄, 1 mM DTT, 10 μM ATP, 0.25-1 μM biotinylated peptide substrate, 0.2-0.8 μCuries per well ³³P-γ-ATP [2000-3000 Ci/mmol]. Assay conditions vary slightly for each protein kinase, for example, insulin receptor kinase requires 10 mM MnCl₂ for activity and Calmodulin-dependent protein kinase requires calmodulin and 10 mM CaCl₂. These assay conditions are known in the art. The reaction mixture was dispensed into the wells of a streptavidin coated Flashplate and 1 μl drug stock in 100% DMSO was added to a 100 μl reaction volume resulting in a final concentration of 1% DMSO in the reaction. Enzyme was diluted in 50 mM Tris-HCl pH=8.0, 0.1% BSA and added to each well. The reaction was incubated for one hour at 30°C in the

presence of compound. After one hour the reaction mix was aspirated from the plate and the plate was washed with PBS containing 100 mM EDTA. The plate was read on a scintillation counter to determine ^{33}P - γ -ATP incorporated into the immobilized peptide. Test compounds were assayed in duplicate at 8 concentrations [100 uM, 10 uM, 1 uM, 100 nM, 10 nM, 1 nM, 100 pM, 10 pM]. A maximum and minimum signal for the assay was determined on each plate. The IC_{50} was calculated from the dose response curve of the percent inhibition of the maximum signal in the assay according to the formula $[\text{max signal} - \text{background} / \text{test compound signal} - \text{background} (100) = \% \text{ inhibition}]$ by graphing the percent inhibition against the log concentration of test compound. Known inhibitor compounds appropriate for the kinase being assayed were also included on each plate.

Definition and Source of Kinase Enzymes

VEGF-R (vascular endothelial growth factor receptor-2) is a fusion protein containing a polyhistidine tag at the N-terminus followed by amino acids 786-1343 of the rat VEGF-R2 kinase domain (GenBank Accession #U93306). CDK1 (cyclin dependent kinase 1) was isolated from insect cells expressing both the human CDK1 catalytic subunit and its positive regulatory subunit cyclin B (New England Biolabs, Beverly, MA, Cat. #6020). CDK2 in complex with cyclin A is commercially available (Upstate Biotech, Lake Placid, NY). The CDK4 complex was composed of a mouse CDK4 protein and a mouse Cyclin D1 protein (The mouse CDK4 protein was genetically fused to an N-terminal Flag-epitope tag and the mouse Cyclin D1 protein was fused with an N-terminal AU-1 epitope tag. The genes encoding these proteins were transferred to commercially available baculoviral vectors. The recombinant CDK4/D1 complex was then made by co-infecting commercially available insect cells with viruses carrying these two constructs). Insulin Receptor Kinase consists of residues 941-1313 of the cytoplasmic domain of the beta-subunit of the human insulin receptor (BIOMOL, Plymouth Meeting, PA, Cat. #SE-195). Protein Kinase A is the catalytic subunit of cAMP dependent protein kinase-A purified from bovine heart (Upstate Biotech, Lake Placid, NY, Cat#14-114). PKC (protein kinase-C) is the gamma or beta isoform of the human protein produced in insect cells (BIOMOL, Plymouth Meeting, PA, Cat. #SE-143). Casein Kinase 1 is a truncation at amino acid 318 of the C-terminal portion of the rat CK1 delta isoform produced in *E.coli* (New England Biolabs, Beverly, MA, Cat.

#6030). Casein Kinase 2 includes the alpha and beta subunits of the human CK2 protein produced in *E.coli* (New England Biolabs, Beverly, MA, Cat. #6010).

Calmodulin Kinase (calmodulin-dependent protein kinase 2) is a truncated version of the alpha subunit of the rat protein produced in insect cells (New England Biolabs,

5 Beverly, MA, Cat. #6060). Glycogen Synthase Kinase-3 is the beta isoform of the rabbit enzyme produced in *E.coli* (New England Biolabs, Beverly, MA, Cat. #6040).

MAP Kinase is the rat ERK-2 isoform containing a polyhistidine tag at the N-terminus produced in *E.coli*. and activated by phosphorylation with MEK1 prior to purification

(BIOMOL, Plymouth Meeting, PA, Cat. #SE-137). ERK-1 protein (Discontinued from

10 Calbiochem). EGFR (epidermal growth factor receptor) is purified from human A431 cell membranes (Sigma, St. Louis, MO, Cat.# E3641). PDGF-R (platelet derived

growth factor receptor) is a fusion protein containing a polyhistidine tag at the N-terminus followed by nucleotides 1874-3507 of the human PDGF-R beta subunit kinase domain (Accession #M21616). The HER2 (human epidermal growth factor receptor-2)

15 construct contains a polyhistidine tag at the N-terminus followed by 24 additional amino acids and begins at amino acid 676 followed by the remainder of the HER2 cytoplasmic domain.

Peptide Substrates

VEGF-R	(Biotin)KHKKLAEGSAYEEV-Amide
CDK1	(Biotin)KTPKKAKKPKTPKKAKKL-Amide
CDK2	(Biotin)KTPKKAKKPKTPKKAKKL-Amide
CDK4	(GST)AminoAcids 769-921 of retinoblastoma
EGF-R	(Biotin)Poly(GT) 4:1
Protein Kinase A	(Biotin)GRTGRRNSI-Amide
PKC	(Biotin)RFARKGSLRQKNV-NH ₂
Casein Kinase 1	(Biotin)KRRRALS(phospho)VASLPGL-Amide
Casein Kinase 2	(Biotin)RREEETEEE-Amide
Calmodulin Kinase	Biotin)KKALRRQETVDAL-Amide
GSK-3	Biotin)KRREILSRRP(phospho)SYR-Amide
MAP Kinase ERK-1	(Biotin)APRTPGGRR-Amide
MAP Kinase ERK-2	(Biotin)APRTPGGRR-Amide
Insulin Kinase	(Biotin)TRDIYETDYRK-Amide

FGF-R2	(Biotin)Poly(GT) 4:1
PDGF-R	(Biotin)KHKKLAEGSAYEEV-Amide
HER2	(Biotin)KHKKLAEGSAYEEV-Amide

The IC₅₀ data for various kinases are shown in Table 2a through Table 2k. IC₅₀ values listed as >10 or >100 indicate no observed 50% inhibition at the highest dose tested for the indicated assay, nor was an inhibition maxima observed. Values shown as ~10 indicate an approximate value based on an observed 50% inhibition. ND means not tested.

Table 2a

Kinase Selectivity

Kinase Assay (IC ₅₀ uM)	Cpd 1	Cpd 2	Cpd 14	Cpd 15	Cpd 16
CDK1	0.006	0.003	0.0045	0.0048	0.021
PKA	>100	>100	5.43	4.26	ND
Caseine Kinase 1	11.16	>100	0.348	0.547	0.214
Caseine Kinase 2	>100	>100	8.05	>100	>100
PKC	ND	>100	ND	ND	ND
ERK 1	ND	ND	>100	ND	ND
ERK 2	19.35	9.48	2.14	5.95	0.39
Calmodulin Kinase 2	>100	>100	60.44	10.53	>100
EGF-R	>100	45.8	1.92	8.44	>100
VEGF-R	0.131	0.366	0.026	0.051	0.0137
Insulin R Kinase	>100	9.8	1.2	2.42	>100
GSK-3	0.041	0.031	0.003	0.0018	0.004
PDGF-R kinase	11.76	10.7	0.189	0.079	0.1
FGF-R2 Kinase	ND	0.269	0.027	ND	ND

Table 2b

Kinase Selectivity

Kinase Assay (IC ₅₀ uM)	Cpd 17	Cpd 23	Cpd 30	Cpd 32	Cpd 33
CDK1	0.0025	0.089	0.017	0.003	0.003
PKA	ND	>100	ND	>100	>100
Caseine Kinase 1	0.643	0.113	1.54	0.181	0.104
Caseine Kinase 2	2.65	>100	7.6	0.527	>10
ERK 2	1.87	1.62	5.93	0.563	>10
Calmodulin Kinase 2	2.8	10.5	88.3	>100	>10
EGF-R	4.13	>100	9.6	>100	>100
VEGF-R	0.027	0.035	0.0406	0.022	0.023
Insulin R Kinase	2.02	>100	4.96	0.123	0.316
GSK-3	0.009	0.016	0.014	0.003	0.004
PDGF-R kinase	0.081	0.629	0.392	0.074	0.039
HER2 Kinase	ND	ND	ND	0.009	0.005

Table 2c

Kinase Selectivity

Kinase Assay (IC ₅₀ uM)	Cpd 34	Cpd 38	Cpd 39	Cpd 51	Cpd 55
CDK1	0.002	0.029	0.012	0.007	0.020
PKA	>100	>100	>100	0.911	>100
Caseine Kinase 1	0.182	6.1	4.1	0.223	9.6
Caseine Kinase 2	>100	>100	>100	1.78	>100
ERK 2	>10	24.2	13.2	0.928	12.9
Calmodulin Kinase 2	>100	>100	>100	0.813	>100
EGF-R	>100	>100	>100	1.1	16.12
VEGF-R	0.068	0.880	0.334	0.019	0.577
Insulin R Kinase	>10	>100	19.4	0.077	>100
GSK-3	0.015	0.122	0.127	0.020	0.040
PDGF-R kinase	0.292	6.37	3.98	0.199	16.18
FGF-R2 Kinase	ND	ND	ND	ND	0.478
HER2 Kinase	ND	ND	ND	0.031	2.19

Table 2d

Kinase Selectivity

Kinase Assay (IC ₅₀ uM)	Cpd 57	Cpd 58	Cpd 61	Cpd 62	Cpd 63
CDK1	0.067	0.014	0.18	0.53	0.079
CDK2	ND	ND	0.049	0.29	0.056
PKA	>100	>100	ND	ND	ND
Caseine Kinase 1	14.0	11.24	ND	ND	ND
Caseine Kinase 2	>100	>100	ND	ND	ND
ERK 2	>100	10.7	ND	ND	ND
Calmodulin Kinase 2	>100	>100	ND	ND	ND
EGF-R	>100	>10	ND	ND	ND
VEGF-R	0.191	0.419	0.072	0.064	0.32
Insulin R Kinase	>100	>100	ND	ND	ND
GSK-3	0.098	0.015	0.055	0.073	0.073
PDGF-R kinase	4.19	8.53	ND	ND	ND
FGF-R2 Kinase	ND	0.096	ND	ND	ND
HER2 Kinase	1.32	0.654	0.82	0.41	0.15

Table 2e

Kinase Selectivity

Kinase Assay (IC ₅₀ uM)	Cpd 64	Cpd 65	Cpd 66	Cpd 69	Cpd 70
CDK1	0.21	0.67	0.0006	0.023	0.035
CDK2	0.20	0.41	ND	ND	ND
CDK4	ND	ND	ND	0.187	0.167
PKA	ND	ND	5.19	46.6	34.2
Caseine Kinase 1	ND	ND	2.75	16.6	35.7
Caseine Kinase 2	ND	ND	>100	>100	>100
ERK 2	ND	ND	1.0	12.5	19.4
Calmodulin Kinase 2	ND	ND	8.99	>100	>100
EGF-R	ND	ND	>10	>100	>100
VEGF-R	0.051	0.18	0.032	0.685	0.911
Insulin R Kinase	ND	ND	>10	45.1	>100
GSK-3	0.021	0.10	0.137	0.147	0.22
PDGF-R kinase	ND	ND	1.58	0.1	16.2
FGF-R2 Kinase	ND	ND	ND	0.365	0.273
HER2 Kinase	0.076	0.79	0.060	0.139	1.23

Table 2f**Kinase Selectivity**

Kinase Assay (IC₅₀ uM)	Cpd 71	Cpd 81	Cpd 82	Cpd 83	Cpd 84
CDK1	3.71	0.018	0.009	0.008	0.004
CDK4	0.129	ND	ND	ND	ND
PKA	>100	>100	>100	>100	2.2
Caseine Kinase 1	>100	6.96	0.354	0.275	0.188
Caseine Kinase 2	>100	>100	>100	>100	1.67
ERK 2	>100	11.68	1.95	>100	1.22
Calmodulin Kinase 2	60.9	>100	>100	>100	>100
EGF-R	>10	>100	>100	>100	>10
VEGF-R	0.43	0.482	0.022	0.040	0.043
Insulin R Kinase	35.3	29.6	1.1	>10	0.172
GSK-3	1.72	0.049	0.025	0.007	0.019
PDGF-R kinase	27	7.76	0.042	0.113	0.280
FGF-R2 Kinase	0.441	0.268	0.089	0.022	0.300
HER2 Kinase	1.30	1.7	0.118	0.013	0.052

Table 2g
Kinase Selectivity

Kinase Assay (IC₅₀ uM)	Cpd 92	Cpd 99	Cpd 103	Cpd 104
CDK1	0.349	0.366	0.007	0.0016
PKA	>100	ND	>100	>100
Caseine Kinase 1	>10	>1	0.322	0.624
Caseine Kinase 2	>100	>100	5.3	>100
PKC	ND	>100	ND	ND
ERK 2	>100	>100	0.845	>100
Calmodulin Kinase 2	19.7	>100	>100	>10
EGF-R	>100	>100	>10	>10
VEGF-R	0.134	0.098	0.045	0.016
Insulin R Kinase	3.08	>100	0.123	2.09
GSK-3	0.021	0.030	0.013	0.020
PDGF-R kinase	0.282	0.385	0.702	0.192
FGF-R2 Kinase	0.242	ND	0.170	0.200
HER2 Kinase	0.056	0.095	0.228	0.202

Table 2h

Kinase Selectivity

Kinase Assay (IC ₅₀ uM)	Cpd 105	Cpd 107	Cpd 108	Cpd 109	Cpd 110
CDK1	0.046	0.014	0.066	0.147	0.022
PKA	>100	>100	>100	>100	>100
Caseine Kinase 1	4.49	0.412	0.816	1.18	0.192
Caseine Kinase 2	>100	>10	>10	>10	>5
ERK 2	18.19	>10	2.39	>10	8.75
Calmodulin Kinase 2	>100	3.43	>10	>100	>100
EGF-R	9.60	0.936	>100	>100	>10
VEGF-R	0.276	0.032	0.030	0.025	0.014
Insulin R Kinase	9.85	0.311	0.811	2.76	0.053
GSK-3	0.082	0.015	0.023	0.039	0.008
PDGF-R kinase	2.20	0.143	0.217	0.413	0.285
FGF-R2 Kinase	0.142	0.235	0.307	0.244	0.153
HER2 Kinase	0.845	0.030	0.042	0.170	0.006

Table 2i

Kinase Selectivity

Kinase Assay (IC ₅₀ uM)	Cpd 113	Cpd 114	Cpd 115	Cpd 116	Cpd 117
CDK1	0.254	0.228	0.313	0.021	0.035
PKA	>100	>100	>100	>100	>100
Caseine Kinase 1	0.318	2.0	9.98	>1	13.46
Caseine Kinase 2	>100	>100	>100	>100	>100
PKC	>100	ND	ND	ND	ND
ERK 2	>100	15.8	>10	>100	>100
Calmodulin Kinase 2	>10	>100	>100	>100	>100
EGF-R	>10	>100	>10	>100	>100
VEGF-R	0.030	0.313	0.467	0.026	0.908
Insulin R Kinase	>10	>100	>10	>100	>100
GSK-3	0.071	0.431	0.391	0.062	1.04
PDGF-R kinase	0.370	13.8	>10	0.302	>100
HER2 Kinase	0.068	1.39	1.44	0.131	5.44

Table 2j
Kinase Selectivity

Kinase Assay (IC₅₀ uM)	Cpd 118	Cpd 119	Cpd 120	Cpd 121	Cpd 123
CDK1	0.330	0.067	0.277	0.099	2.05
PKA	>100	>100	>100	>100	>100
Caseine Kinase 1	>100	0.757	>10	>10	>100
Caseine Kinase 2	>100	>100	>100	>100	>100
PKC	ND	>100	ND	ND	ND
ERK 2	>100	>100	>100	>100	>100
Calmodulin Kinase 2	>100	>100	>100	>100	>100
EGF-R	>100	0.159	>10	>10	>100
VEGF-R	0.397	0.057	0.082	0.027	5.52
Insulin R Kinase	>100	0.159	>100	>100	>100
GSK-3	0.159	0.006	0.018	0.029	3.01
PDGF-R kinase	>100	>10	0.822	0.394	>100
HER2 Kinase	>10	1.0	1.0	0.717	>100

Table 2k
Kinase Selectivity

Kinase Assay (IC₅₀ uM)	Cpd 124	Cpd 125	Cpd 126	Cpd 127	Cpd 128
CDK1	2.2	>100	>100	>100	0.003
CDK2	1.7	7.3	>100	>100	ND
PKA	ND	ND	ND	ND	>100
Caseine Kinase 1	ND	ND	ND	ND	8.97
Caseine Kinase 2	ND	ND	ND	ND	>100
ERK 2	ND	ND	ND	ND	2.07
Calmodulin Kinase 2	ND	ND	ND	ND	13.2
EGF-R	ND	ND	ND	ND	>100
VEGF-R	4.8	>100	>100	>100	0.118
Insulin R Kinase	ND	ND	ND	ND	2.65
GSK-3	3.0	>100	>100	>100	0.094
PDGF-R kinase	ND	ND	ND	ND	1.91
HER2 Kinase	0.82	>100	~100	>100	0.11

Example 3

Assay to Measure Inhibition of Cell Proliferation

- 5 The ability of a test compound to inhibit the proliferation of cell growth was determined by measuring incorporation of ¹⁴C-labelled thymidine into newly synthesized DNA within the cells. This method was used on cell lines derived from carcinomas originating from several tissues such as **HeLa** cervical adenocarcinoma (American Type Culture Collection (ATCC), Virginia, Cat. #CCL-2), **A375** malignant
- 10 melanoma (ATCC CRL-1619), **SK-OV-3** ovarian adenocarcinoma (ATCC HTB-77) **HCT-116** colon carcinoma (CCL-247), **PC-3** prostate adenocarcinoma (ATCC CRL-1435), and **MDA-MB-231** (Xenogen Corp.) In this way the effect of a compound on cell growth of cells with many different phenotypes can be determined. Cells were trypsinized and counted and 3000-8000 cells were added to each well of a 96-well
- 15 CytoStar tissue culture treated scintillating microplate (Amersham #RPNQ0160) in complete medium in a volume of 100 µl. Cells were incubated for 24 hours in complete medium at 37°C in an atmosphere containing 5% CO₂.

Next, 1 µl of test compound in 100% DMSO was added to the wells of the plate.

DMSO only was added to control wells. Cells were incubated for 24 more hours in complete medium at 37°C in an atmosphere containing 5% CO₂. Methyl ¹⁴C-thymidine 56 mCi/mmol (NEN #NEC568 or Amersham #CFA532) was diluted in complete medium and 0.2 uCi/well was added to each well of the CytoStar plate in a volume of 20 ul. The plate was incubated for 24 hours at 37°C plus 5% CO₂ in drug plus ¹⁴C-thymidine. The contents of the plate were discarded into a ¹⁴C radioactive waste container by inverting the plate and the plate was washed twice with 200 µl PBS. 200 µl of PBS is added to each well. The top of the plate was sealed with a transparent plate sealer and a white plate backing sealer (Packard #6005199) was applied to the bottom of the plate. The degree of methyl ¹⁴C-thymidine incorporation was quantified on a Packard Top Count.

Table 3
Inhibition of Cell Proliferation (IC₅₀ nM)

Cpd	Cell Line					
	HeLa	HCT-116	SK-OV-3	MDA-MB-231	PC-3	A375
1	284	254	750	587	119	447
14	550	1940	727	756	157	26460
15	91	127	242	550	107	247
16	263	213	2110	ND	368	942
17	215	309	3900	ND	294	4970
23	1180	376	1420	868	859	424
30	215	1930	5750	ND	951	8240
32	71	26	ND	131	30	ND
33	72	27	ND	171	37	ND
34	707	996	ND	898	626	ND
35	663	172	ND	1140	231	ND
38	4560	2270	ND	6760	2750	ND
39	270	1410	ND	2910	625	ND
51	220	ND	ND	ND	57	333
57	339	95	ND	ND	ND	113
58	186	1,270	ND	ND	362	981
66	35	20	ND	ND	ND	92
69	218	1,720	ND	ND	8	441

70	196	1,580	ND	ND	11	1,100
71	1,920	ND	ND	ND	25	ND
80	880	ND	16,300	ND	272	ND
81	189	778	348	ND	25	1,770
82	245	ND	921	ND	15	ND
83	122	192	ND	ND	12	556
84	142	ND	461	ND	23	ND
92	269	ND	ND	ND	1,120	ND
99	3,350	ND	ND	ND	1,690	ND
103	62	75	ND	ND	ND	115
104	186	41	ND	ND	ND	108
105	626	320	ND	ND	ND	652
107	177	95	ND	ND	ND	113
108	221	76	ND	ND	ND	259
109	479	51	ND	ND	307	ND
110	237	187	ND	ND	ND	239
113	242	281	281	ND	ND	ND
114	2,530	1,380	ND	ND	ND	1,690
115	676	486	ND	ND	ND	529
116	380	349	ND	ND	ND	639
117	2,060	1,120	ND	ND	ND	2,190
118	1,940	1,170	ND	ND	ND	1,620
119	146	117	ND	ND	ND	199
120	978	334	ND	ND	ND	259
121	310	608	ND	ND	ND	215
123	28,500	4,140	ND	ND	ND	>10,000
128	128	910	ND	ND	ND	968

Example 4

In Vivo Models – Inhibition of Tumor Growth

5 The *in vivo* effect of a compound on the growth of human tumor cells can be evaluated by implanting human tumor cells into the hindflank of athymic mice and administering test compound to the mice. Human tumor cells originating from a variety of different tumor types, such as A375 human melanoma cells, are implanted subcutaneously into

the hindflank of male athymic mice (Charles River) and allowed to establish a sizeable tumor for 6-10 days as determined by caliper measurements. Test compound is then administered by injecting the compound formulated in an appropriate vehicle intraperitoneally into the mice once a day for 30 days. The test compound can also be administered by other routes such as orally, sub cutaneously or by intravenous infusion. The size of the tumor in this study is measured every four days and the degree of inhibition is determined by comparing drug-treated animals to animals that are injected with vehicle only

- 5
- 10 The synergistic action or enhancement of conventional chemotherapeutic agent by a test compound can also be determined with this model by comparing animals treated with the standard therapy alone to animals treated with test compound plus the same standard therapy. An additive effect on the delay of tumor growth will be observed if synergistic action due to test compound is occurring.

15

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and modifications as come within the scope of the following claims and their equivalents.

20

Throughout this application, various publications are cited. The disclosure of these publications is hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.